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Insulin Antagonists, Insulin Antibodies and Insulin Resistance
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Clinical Studies

Role of Hageman Factor in the Initiation of Clotting by Glass. Evidence that Glass Frees Hageman Factor from Inhibition
OSCAR D. RATNOFF AND JEROLD M. ROSENBLUM 160

The specific blood clotting factor, which promotes rapid coagulation when shed blood is placed in glass tubes, is shown in this interesting study to be absent from the plasma of patients with the Hageman trait, and for this and other cogent reasons is identified with the Hageman factor. The Hageman factor presumably is an inactive state in normal plasma, if the fluidity of the blood is to be maintained, because, it is suggested, of the presence of specific inhibitor. Hageman factor, once activated, is rapidly destroyed by an enzyme. The authors speculate about possible implications in respect to thromboembolism.

Quantitative Measurement of Gastrointestinal Blood Loss. I. The Use of Radioactive Cr^{51} in Patients with Gastrointestinal Hemorrhage
FRANKLIN G. EBAUGH, JR., TED CLEMENS, JR., GERALD RODNAN AND R. E. PETERSON 169

By application of an ingenious Cr^{51} labeling method for determining the amount of blood lost in the feces, combined with intestinal intubation for localization of the bleeding site, the authors were able to establish a correct diagnosis in eight of nine cases of anemia of obscure etiology. The normal maximal blood loss in the feces was found to approximate 1.2 ± 0.5 ml. per day. The unreliability of the benzidine test for blood in the stools, as compared with that for hemoglobin in aqueous solution, is indicated by appropriate data. Since the study deals with quantitative measurements in a clinically important area in which such measurements are much needed, it will be found informative and helpful.

Polycythemia and Renal Carcinoma. Report of Ten New Cases, Two with Long Hematologic Remission Following Nephrectomy
ALBERT DAMON, DONALD A. HOLUB, MEYER M. MELICOW AND AURELIO C. USON 182

The puzzling occasional association of polycythemia with renal carcinoma, long known, is here subjected to searching and informative analysis of ten cases collected by the authors, and the cases

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previously reported in the literature. The results leave no doubt that the association is not wholly coincidental. It is made clear that the blood anomaly involves only an erythrocytosis (not accompanied by marked splenomegaly, leukocytosis or thrombocytosis), and that this erythrocytosis is causally related to the renal tumor because it is apt to disappear after surgical removal of the neoplasm. Since the kidney appears normally to elaborate an erythropoietic substance, perhaps overproduction of this substance by the enlarged kidney is responsible for the exaggerated erythropoiesis. In any event, hematuria in patients with polycythemia should not be dismissed as due to renal infarction but should stimulate search for possible renal carcinoma, as the authors emphasize.

Non-Addisonian Megaloblastic Anemia. The Intermediate Megaloblast in the Differential Diagnosis of Pernicious and Related Anemias

HUGH FUDENBERG AND SOLOMON ESTREN 198

The "intermediate" megaloblast, a transitional form of megaloblast with atypical features, is found in a variety of non-Addisonian macrocytic anemias, as illustrated herein by four cases; indeed this feature is distinctive enough to aid in the differentiation from Addisonian pernicious anemia. It is suggested that intermediate megaloblastic erythropoiesis does not reflect a relative deficiency of vitamin B_{12} or other erythrocyte maturation factors, as has been supposed, but is due to a concomitant defect in iron stores or iron metabolism, resulting in inadequate "hemoglobinization" of megalocyte precursors.

Agranulocytosis Following Administration of Phenothiazine Derivatives

ANTHONY V. PISCIOTTA, SHIRLEY EBBE, EDWARD J. LENNON, GLORIA OLSEN METZGER AND FREDERICK W. MADISON 210

The authors describe the occurrence of granulocytopenia in eighteen patients with mental disease who received chlorpromazine. Granulocyte precursors disappeared from the bone marrow, gradually returning when the drug was discontinued, with full restoration to normal peripheral smears. The only accompanying clinical manifestations were usually mild infections such as sore throat, presumably because the granulocytopenia was recognized early by frequent blood counts and prompt investigation of infections. Bone marrow depression was observed after prolonged treatment with large cumulative doses, and there were no clinical evidences of allergic disease in the patients affected. No leukagglutinins or leukolysins could be detected in *in vitro* tests; immunoallergic factors do not appear to be responsible for this type of drug reaction.

Tricuspid Regurgitation Masquerading As Mitral Regurgitation in Patients with Pure Mitral Stenosis

JOSEPH F. URICCHIO, LAMBERTO BENTIVOGLIO, RICHARD GILMAN AND WILLIAM LIKOFF 224

The authors demonstrated, by means of clinical observation, phonocardiography, cardiac catheterization and ventriculography (right and left), the presence of tricuspid regurgitation simulating mitral insufficiency in five cases of mitral stenosis. Since mitral insufficiency of sufficient degree is a

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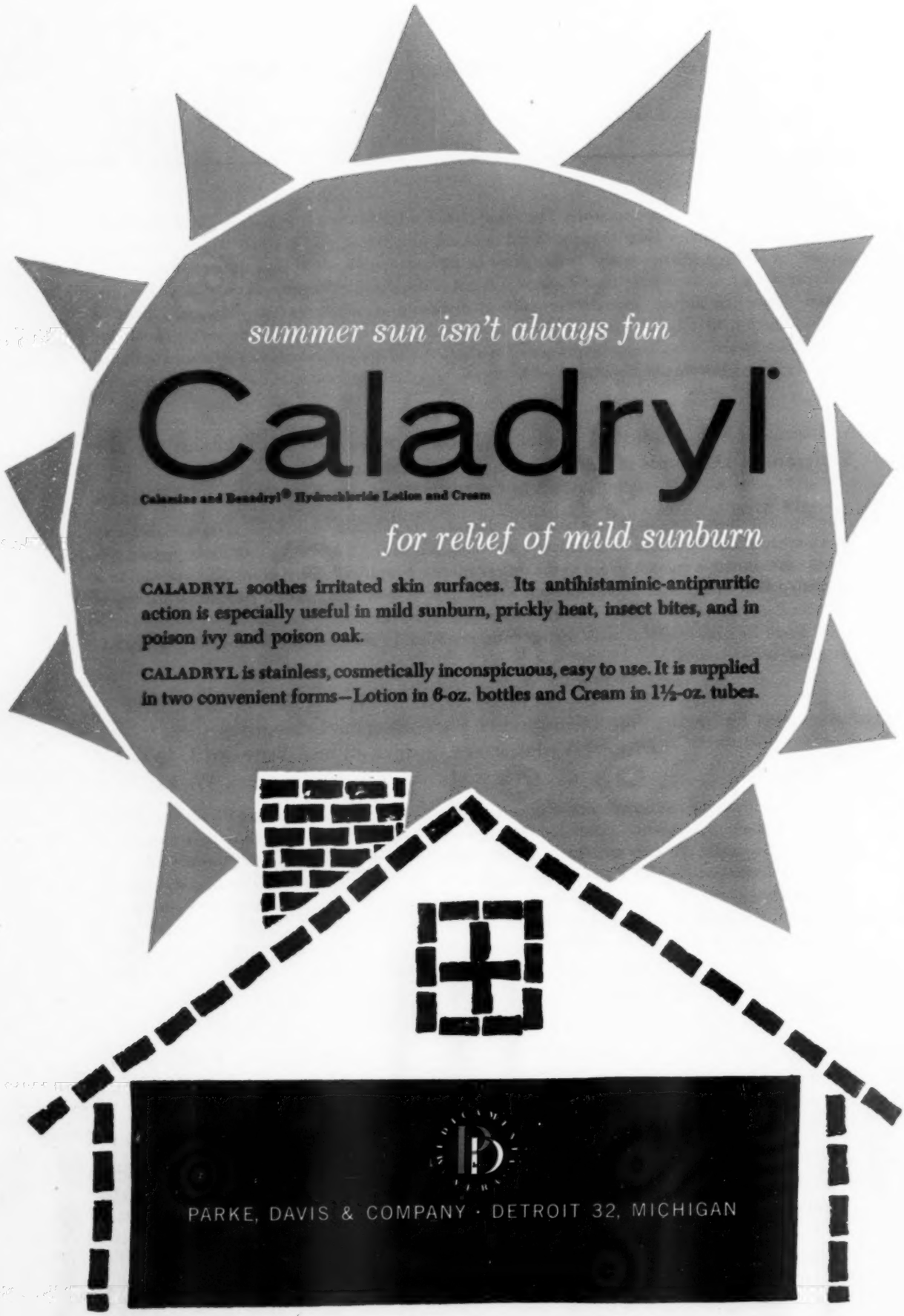
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contraindication to mitral commissurotomy, it is apparent that this cause of confusion, which probably occurs not infrequently, may lead to mistaken denial of surgery to patients in whom it might well be beneficial.

The Fate of Human Aortic Grafts. Autopsy Findings in Two Patients with Functioning Homografts for Eleven and Thirty-two Months

GRAHAM KNOX AND CHARLES F. BEGG 231

Because of the widespread employment of homologous arterial and aortic implants, the ultimate fate of these grafts has become a matter of great significance. Two patients with functioning homografts present for eleven and thirty-two months are described in this paper. The integrity of the elastic layer of these implanted arterial segments apparently served as an important strut for envelopment by host tissue.

Reviews

Bagassosis. A Review, with Further Historical Data, Studies of Pulmonary Function, and Results of Adrenal Steroid Therapy

HOWARD A. BUECHNER, AMOS L. PREVATT, JORDAN THOMPSON AND OSCAR BLITZ 234

Bagassosis, a characteristic lung disease resulting from inhalation of bagasse dust (the fibrous material of sugar cane remaining after extraction of the juice), is here described interestingly and in detail. The disorder appears to be essentially a form of bronchiolitis, with dyspnea, fever, cough, hemoptysis, weakness and weight loss as the presenting symptoms. Chest films, like the symptomatology, simulate pulmonary tuberculosis, with miliary spread. Pulmonary function tests indicated alveolar hypoventilation. A striking response to corticosteroids and corticotrophin was obtained in a severely ill patient, suggesting further trial of this therapy.

Sociologic, Psychologic and Metabolic Observations on Patients in the Community of a Metabolic Ward

WILLIAM W. SCHOTTSTAEDT, RUTH H. PINSKY, DAVID MACKLER AND STEWART WOLF 248

Because this report describes more clearly and with greater insight what every discerning physician must sense in any hospital community of patients, it makes absorbing and rewarding reading. The (metabolic) ward was found to have "the special characteristics of a well defined community with its own pressures, values, prestige points and taboos." How these affect metabolic balances, under conditions otherwise as rigidly controlled as is humanly possible, is the specific substance of the report.

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- postoperatively
- in pregnancy when vomiting is persistent
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Seminar on the Brain

Pathological Effects of Cerebral Anoxia . . . . . .Leo Krainer 258

Considering the morphologic effects of cerebral anoxia on the central nervous system, it is apparent that these vary according to pathogenesis, degree and duration of anoxia, and a variable vulnerability to anoxia of different areas which in turn depends upon a number of factors, many not yet elucidated. These aspects are discussed in relation to both generalized and local cerebral anoxia.

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Clinico-pathologic Conference (Washington University School of Medicine).

Case Reports

A Case of Massive Edema in Association with an Aldosterone-Secreting Adrenocortical Adenoma

Eric J. Ross, Jean Crabbé, Albert E. Renold, Kendall Emerson, Jr. and George W. Thorn 278

A case of edema of unusual interest, studied intensively over a period of twelve years. The data indicate a defect in capillary permeability, excessive aldosterone excretion, marked retention of sodium, and an adenoma in one adrenal gland, all factors contributing to the edema. How these factors are related was (and remains) a difficult problem. The authors' views on this point are of considerable interest.

The Development of Myasthenia Gravis after Removal of Thymoma

Robert A. Green and Carl B. Booth 293

An interesting and well studied case, informatively discussed.

An Hereditary Anemia with Hemochromatosis. Studies of an Unusual Hemopathic Syndrome Resembling Thalassemia. . Armand P. Gelpi and Norman Ende 303

It may be difficult to determine to what degree some of the findings in the primary case are related to the therapeutic measures employed, but the authors have made a careful study of the patient and his family, and the results are certainly of unusual interest. The disorder is related by the authors to a hereditary form of anemia originally described by Cooley, simulating but clearly not thalassemia.

Porphyria Cutanea Tarda without Skin Lesion in an American Negro

John T. Galambos 315

An interesting case.

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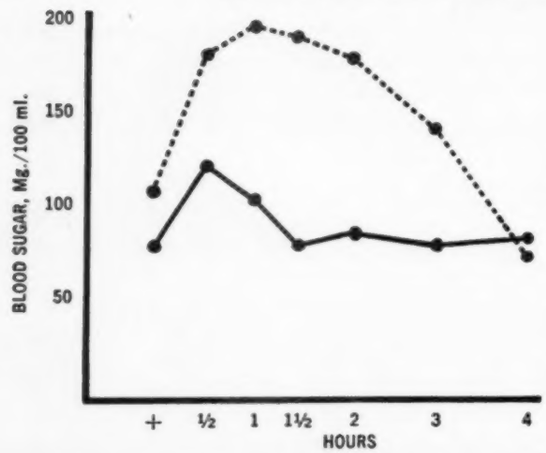
AN AMES CLINIQUICK

CLINICAL BRIEFS FOR MODERN PRACTICE

HYPERGLYCEMIC EFFECT OF CORTICOSTEROIDS[3]



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Sources—1. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, p. 156. 2. Hennes, A. R.; Wajchenberg, B. L.; Fajans, S. S., and Conn, J. W.: Metabolism *6*:339, 1957.

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Right Atrial Myxoma. A Clinical Study of a Patient in Whom Diagnosis Was Made by Angiocardiography during Life. (Surgically Removed)
HAROLD A. LYONS, JOHN J. KELLY, JR., NATHANIEL NUSBAUM AND CLARENCE DENNIS 321

The possibility of surgical removal of myxoma of the heart has increased interest in the problems of diagnosis during life. These are exemplified by the case herein reported, which clinically simulated tricuspid stenosis. The correct diagnosis was made by angiocardiography.

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1. *Friedlander, H. S.: The role of atarazics in cardiology. Am. J. Card.* **1**:395, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957*

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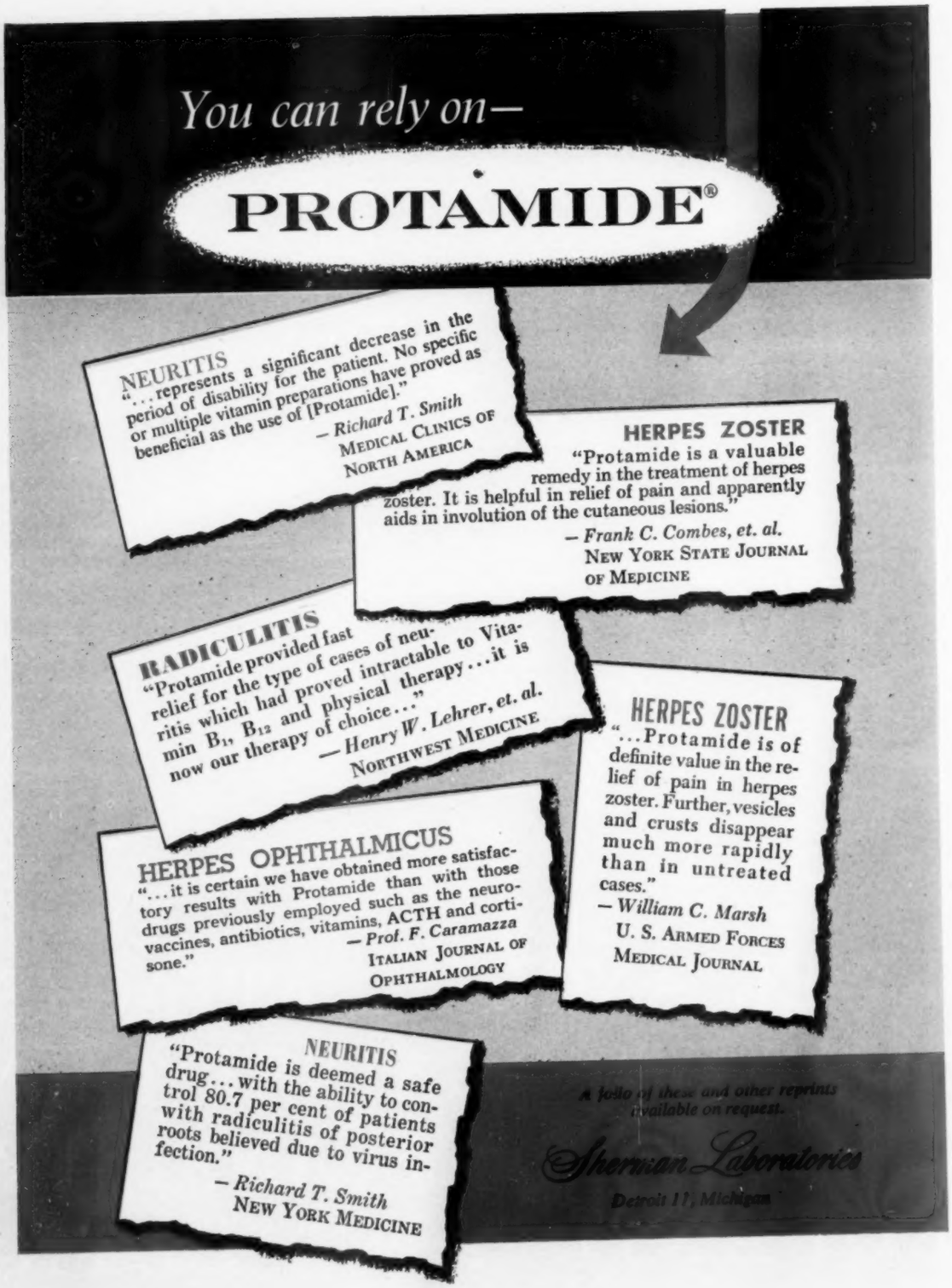
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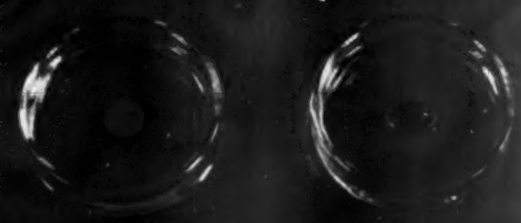

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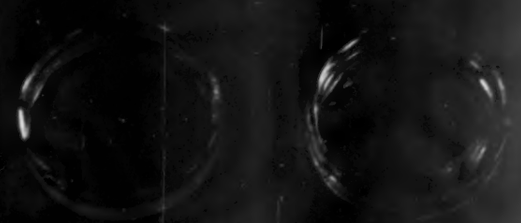

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1. Murphree, H. B., Jr.; Jenney, E. H., and Pfeiffer, C. C.: 2-Dimethylaminoethanol as a Central Nervous System Stimulant, Presented before Assoc. for Research in Nervous and Mental Disease, New York, Dec. 12-14, 1957. To be published.

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2. Lemere, F., and Lasater, J. H.: Am. J. Psychiat. *114*:655 (Jan.) 1958.

In Learning Problems—Some of the children with reading problems and other learning defects have improved markedly during their treatment with 'Deaner'.

3. Oettinger, L., Jr.: Presented before the American Encephalographic Society Meeting, Atlantic City, June 14, 1958. To be published.

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Following the discovery of ORINASE, years of careful, experimental control of diabetic patients revealed the safety and wide area of efficacy of this new therapeutic agent. Then, one year ago, ORINASE was made available for general clinical practice. Today, in one year, over 300,000 patients have assumed a more normal way of life, with the smooth oral control of hyperglycemia afforded by ORINASE.

With these "hundreds-of-thousands of patient years" of therapy as evidence, it can truly be stated that the long sought-for breakthrough has been achieved and that we have entered the ORINASE EPOCH.

*TRADEMARK, REG. U.S. PAT. OFF.—TOLBUTAMIDE, UPJOHN

BREAKTHROUGH:

Here are the areas of the breakthrough:

THE ORINASE EPOCH

BREAKTHROUGH FOR THE PATIENT

Freed from the encumbrances of needle syringe and sterilization, and freed from the tensions caused by worry about potential hypoglycemic reaction, the patient on Orinase can look forward to a more normal type of life in which his metabolic disorder is not complicated by the paraphernalia of injection.

For the newly discovered patient, the diagnosis of diabetes is no longer a commitment to a long sentence of injections. Families of diabetics can now assume a more normal way of life, unimpeded by social and economic disabilities and the personal demands of the metabolic invalid. This new era has opened for the majority of diabetics. Those most responsive have had onset of diabetes after 40 years of age and, if on insulin, generally require less than 40 units daily.

BREAKTHROUGH FOR THE PHYSICIAN

"Orinase-responsive" patients, as a group, usually enjoy a superior quality of control. With Orinase, the management of diabetes is smoother, associated with a feeling of greater stability and well-being, and free from the danger of hypoglycemic shock. Patients are more cooperative and can assume occupations from which hormonal therapy might disqualify them.

New diabetics are easier to indoctrinate and to manage. Mild diabetics, who either personally object to insulin or whose diabetes is so mild as to make one hesitate to add insulin to the regimen, are both excellent candidates for Orinase.

BREAKTHROUGH FOR METABOLIC INVESTIGATORS

It has been shown that Orinase corrects hyperglycemia by stimulating the elaboration and release of *native* endogenous insulin. Its administration in the presence of functional beta cells results in changes in fat and protein metabolism known to be the physiologic resultants of insulin activity. More recently several investigations have demonstrated that the effects of Orinase upon hepatic glucose release are none other than those of endogenously produced or endoportally administered insulin. These observations have been followed by the further realization that the liver may play a primary physiologic role in the mechanisms of insulin action. Experience with Orinase suggests a classification of diabetics into two apparently distinct groups—the Orinase-responsive or the "Orinase-positive" diabetics and the "Orinase-negative" diabetics. It remains to be determined whether these will prove to be distinct clinical entities.

Upjohn

in **diabetic retinopathy**

and other eye disorders involving capillary fault

C.V.P.®

exclusive water-soluble citrus bioflavonoid compound combined with ascorbic acid

... improved visual acuity
and cleared hemorrhages more rapidly

C.V.P. helps to correct abnormal capillary permeability, fragility and resultant bleeding and thus acts as "a valuable therapeutic aid in the management of certain ocular diseases,"[1] as evidenced in a series of 89 patients suffering from various ophthalmic disorders such as:

diabetic retinopathy
idiopathic retinal hemorrhage
senile macular degeneration

Each C.V.P. capsule or teaspoonful (5 cc.) of syrup provides
CITRUS BIOFLAVONOID COMPOUND . . . . 100 mg.
ASCORBIC ACID (vitamin C) . . . . . 100 mg.

bottles of 100, 500, and 1000 capsules; 4 oz., 16 oz. and gallon syrup.

1. Ralph, F. T.: Eye, Ear, Nose and Throat Monthly, Feb. 1958.

samples and literature from

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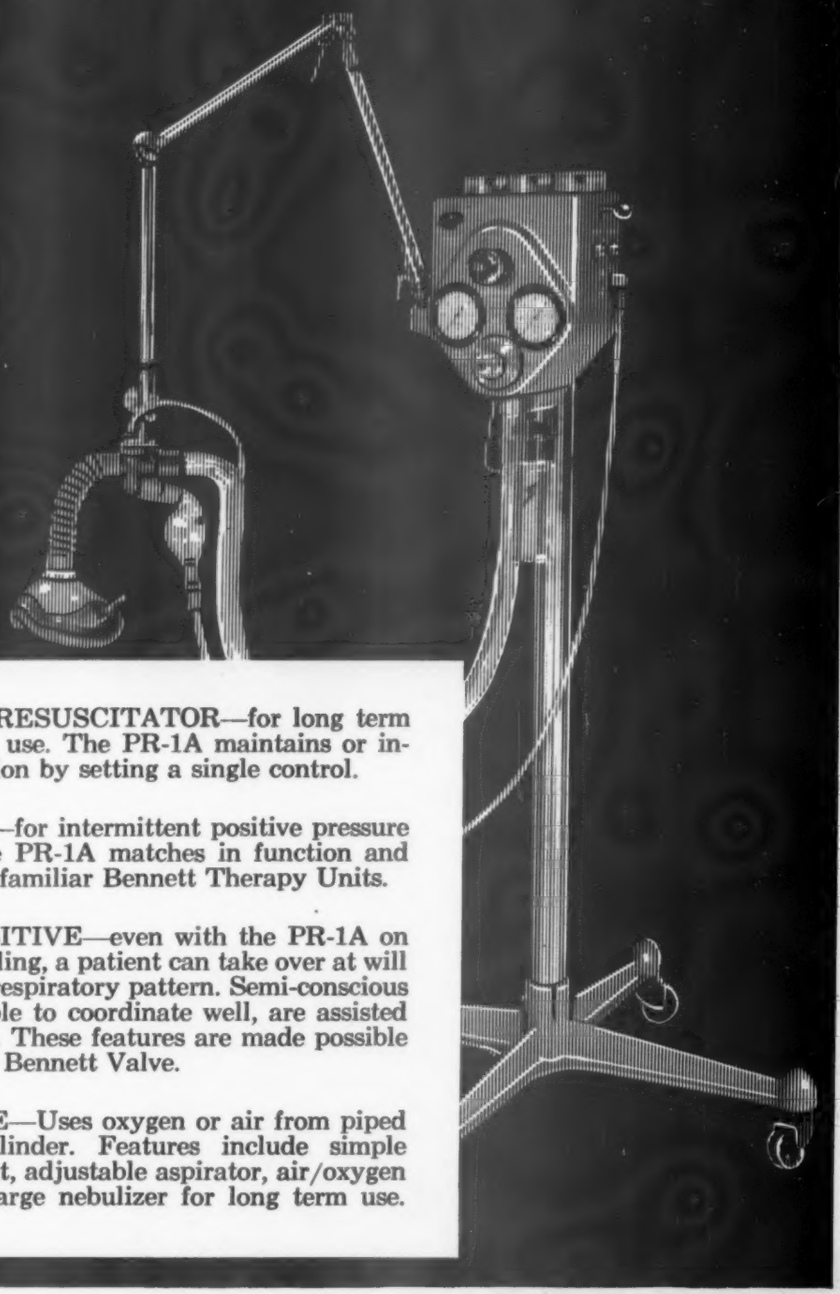
(Arlington-Funk Laboratories, division) • 250 E. 43rd Street, New York 17, N. Y.

BENNETT MODEL PR-1A RESPIRATOR



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- IPPB UNIT—for intermittent positive pressure breathing, the PR-1A matches in function and operation the familiar Bennett Therapy Units.
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Model PR-1A Respiration Unit $550.00, FOB Los Angeles

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Distributed East of the Continental Divide by Puritan Compressed Gas Corp.

PROVED ANTIBIOTIC DIFFUSION

Tetrex®
Tetracycline Phosphate Complex **CAPSULES**

PROVIDES
HIGH
TETRACYCLINE
CONCENTRATIONS
IN BODY FLUIDS
AND TISSUES

**FOR INTENSIFIED
BROAD-SPECTRUM
ANTIBIOTIC CONTROL**

mother's milk
0.45 mcg./ml.[1]
(at 2 hrs. 20 min.
after 500 mg. dose)

portal vein
4.8 mcg./ml.[1]
(at 2 hrs.
after 500 mg. dose)

bile
33.5 mcg./ml.[2]
(max. av.—6 hrs.
after 2nd 500 mg. dose)

amniotic fluid
0.88 mcg./ml.[1]
(at 10 hrs.
after 500 mg. dose)

urine
50.3 mcg./ml.[3]
(av. concentration
following 500 mg. dose)

1. Shidlovsky, B. A., et al.: In Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 459.
2. Pulaski, E. J., and Isokane, R. K.: Antibiotic Med. 4:408, 1957.
3. Buckwalter, F. H., and Cronk, G. A.: Ibid. 5:46, 1958.

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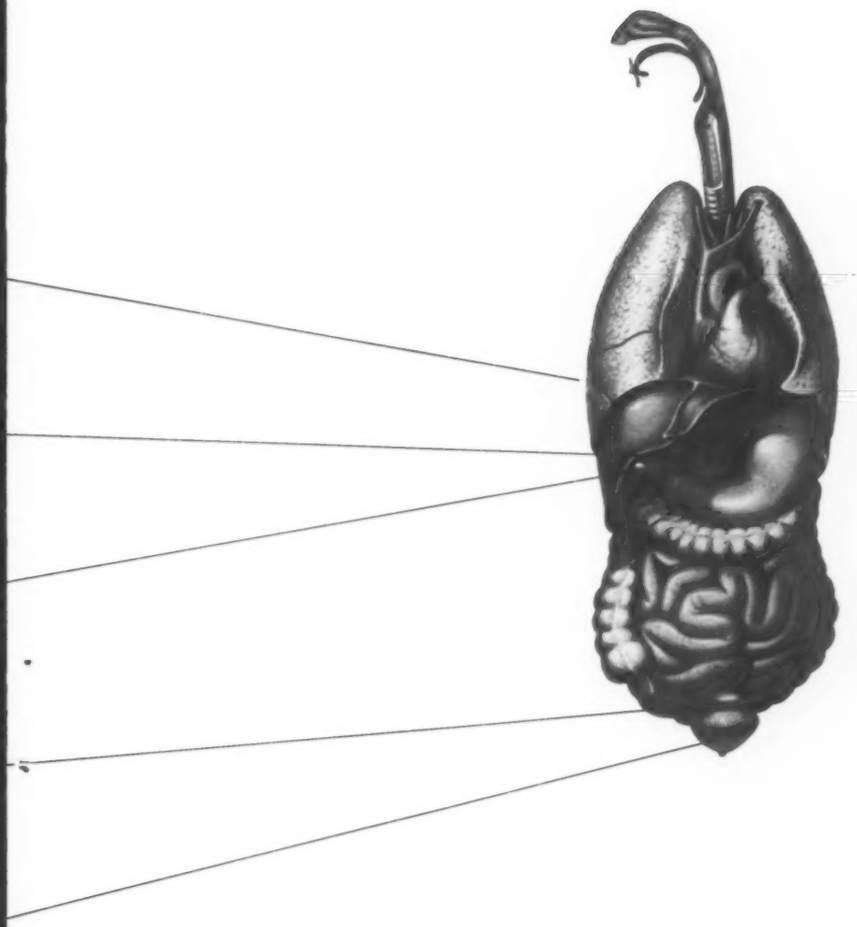

Tetrex®

Tetracycline Phosphate Complex 250 • 100 mg. CAPSULES

'DUANAT' REPRODUCTION. PAT. PENDING.

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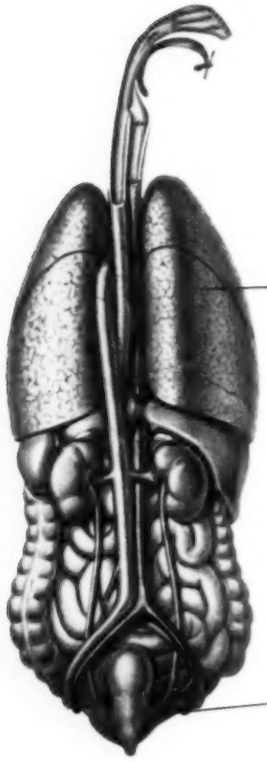

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Tetracycline Phosphate Complex 250-100 mg. CAPSULES

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ACTION AT THE POINT OF INFECTION

in 232 respiratory infections:
"All patients infected with tetracycline-sensitive organisms responded satisfactorily . . ."[1]

in 94 dermatologic infections:
"88 per cent . . . obtained excellent or good improvement . . ."[2]

in 30 g.u. infections:
effective in all cases of urethritis, cystitis, pyuria.[1,3]

in 103 soft-tissue infections:
"marked decrease in morbidity and hospitalization" and "incidence and magnitude of the [surgical] procedures was lessened."[4]

Tetrex®

Tetracycline Phosphate Complex
U.S. Pat. 2,791,609

CAPSULES

For antibiotic action at the foci of infection, TETREX provides rapid, uniformly successful control of tetracycline-sensitive organisms...as demonstrated by the results in 826 systemic and local infections[1-4] (including those illustrated).

A pure antibiotic compound, not a mixture —"more rapidly and completely absorbed . . ."[5] than tetracycline HCl, providing fast, high concentrations in body fluids and tissues.

Highly flexible in dosage . . . equally effective on b.i.d. (500 mg.) or q.i.d. (250 mg.) schedule[1-3] with equally excellent toleration.

"can be safely and successfully administered..." to OB patients and nursing mothers—"no deleterious effect on the infants in utero or on the breast-fed infants."[6]

SUPPLIED: TETREX Capsules containing the equivalent of 250 mg. tetracycline HCl activity; bottles of 16 and 100. *New* TETREX Pediatric Capsules containing the equivalent of 100 mg. tetracycline HCl activity; bottles of 25 and 100.

1. Cronk, G. A., et al.: In Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 397. 2. Rein, C. R., and Fleischmajer, R.: Antibiotic Med. 4:422, 1957. 3. Putnam, L. E.: Ibid. 4:470, 1957. 4. Prigot, A., et al.: Ibid. 4:287, 1957. 5. Council on Drugs, A.M.A.: J.A.M.A. 166:50, 1958. 6. Shidlovsky, B. A., et al.: In Antibiotics Annual 1957-1958, *vide supra.*, p. 459.

POSITIVE RESULTS AGAINST MANY GRAM-NEGATIVE INVADERS

CHLOROMYCETIN®

COMBATS MOST CLINICALLY IMPORTANT PATHOGENS

Gram-negative organisms, involved in many stubborn infections, demonstrate high *in vitro* sensitivity to CHLOROMYCETIN.[1-8]

The efficacy of CHLOROMYCETIN against these troublesome invaders is borne out *in vivo* in such infections as infantile gastroenteritis,[9] urinary tract infections,[10] the septicemic and focal forms of salmonellosis,[11] and Friedländer's pneumonia.[12]

CHLOROMYCETIN is available in a variety of forms, including Kapseals,® of 250 mg., bottles of 16 and 100.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Schneierson, S. S.: *J. Mt. Sinai Hosp.* **25**:52, 1958. (2) Waisbren, B. A.: *Wisconsin M. J.* **57**:89, 1958. (3) Ritts, R. E., Jr.; Mao, F. H., & Favour, C. B.,in Welch, H., & Marti-Ibanez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 774. (4) Rhoads, P. S.: *Postgrad. Med.* **21**:563, 1957. (5) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M.A.J.* **77**:844, 1957. (6) Hasenclever, H. F.: *J. Iowa M. Soc.* **47**:136, 1957. (7) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* **29**:159, 1957. (8) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* **99**:744, 1957. (9) Derham, R. J., & Rogerson, M. M.: *J. Dis. Child.* **93**:113, 1957. (10) Murphy, J. J., & Rattner, W. H.: *J.A.M.A.* **166**:616, 1958. (11) Rabe, E. F.: *Pennsylvania M. J.* **61**:209, 1958. (12) Rosenthal, I. M.: *GP* **17**:77 (March) 1958.

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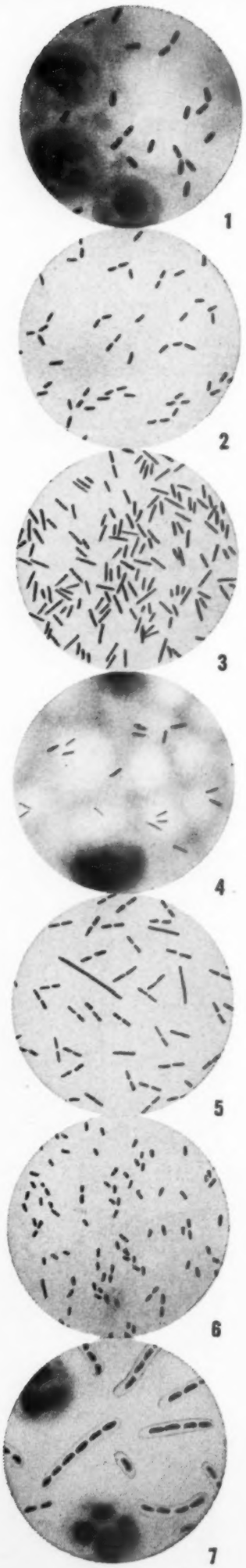
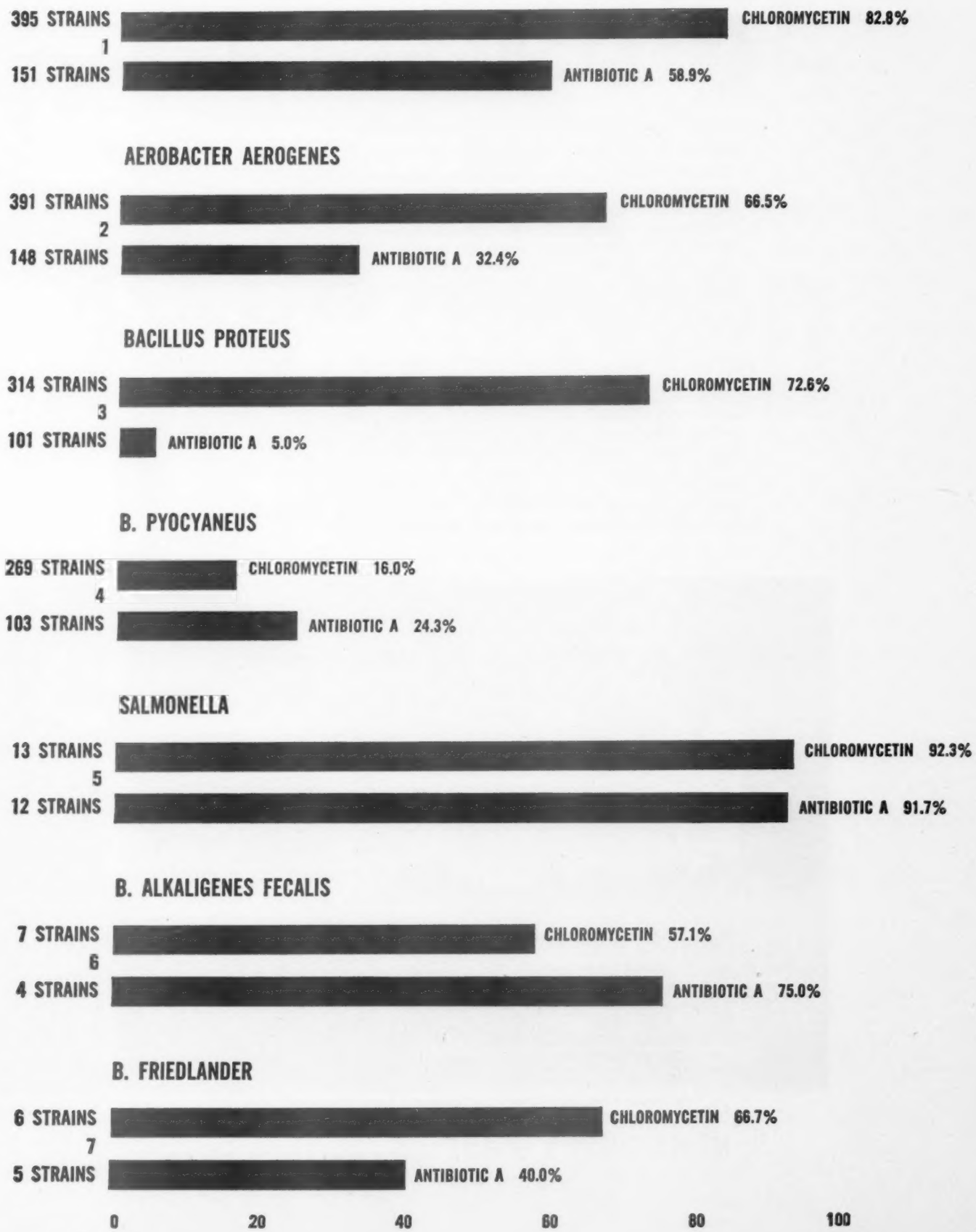


IN VITRO SENSITIVITY OF SEVEN GRAM-NEGATIVE PATHOGENS TO CHLOROMYCETIN AND TO ANOTHER WIDELY USED ANTIBIOTIC*



*Adapted from Schneierson.[1]

Investigator

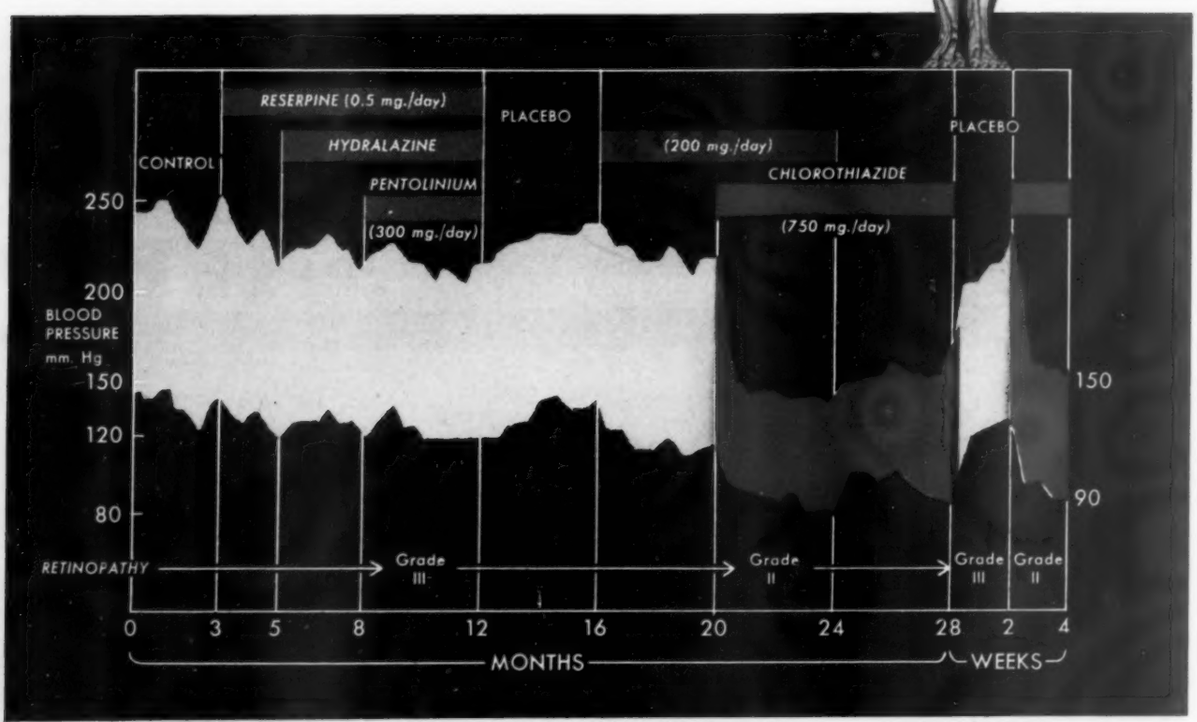
after investigator reports

Wilkins, R. W.: New England J. Med. **257**:1026, Nov. 21, 1957.

"Chlorothiazide added to other antihypertensive drugs reduced the blood pressure in 19 of 23 hypertensive patients." "All of 11 hypertension subjects in whom splanchnicectomy had been performed had a striking blood pressure response to oral administration of chlorothiazide." ". . . it is not hypotensive in normotensive patients with congestive heart failure, in whom it is markedly diuretic; it is hypotensive in both compensated and decompensated hypertensive patients (in the former without congestive heart failure, it is not markedly diuretic, whereas in the latter in congestive heart failure, it is markedly diuretic). . . ."

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. **166**:137, Jan. 11, 1958.

"Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction [16%] of blood pressure." "The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple 'rule of thumb' oral dosage schedules."



In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

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the effectiveness of 'DIURIL' (CHLOROTHIAZIDE) in Hypertension

as simple as 1-2-3

1 **INITIATE THERAPY WITH 'DIURIL'.** 'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day.

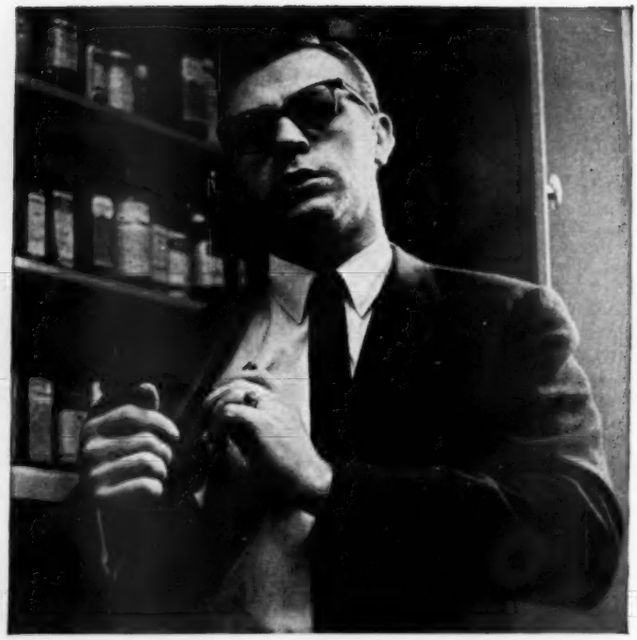
2 **ADJUST DOSAGE OF OTHER AGENTS.** The dosage of other antihypertensive medication (reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response. If the patient is established on a ganglionic blocking agent (e.g., 'INVERSINE') this should be continued, but the total daily dose should be immediately reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

3 **ADJUST DOSAGE OF ALL MEDICATION.** The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

SUPPLIED: 250 mg. and 500 mg. scored tablets 'DIURIL' (chlorothiazide); bottles of 100 and 1,000.

'DIURIL' is a trade-mark of Merck & Co., Inc.

Smooth, more trouble-free management of hypertension with 'DIURIL'



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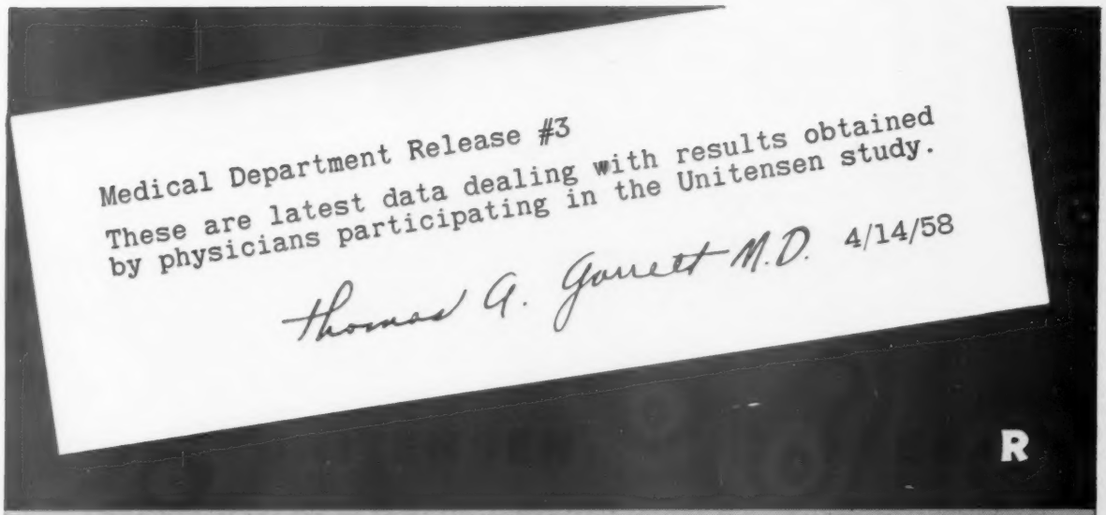
LIPO GANTRISIN® ACETYL—BRAND OF ACETYL SULFISOXAZOLE


Medical Department Release #3
These are latest data dealing with results obtained by physicians participating in the Unitensen study.
Thomas G. Gorrett M.D. 4/14/58
R

SUMMARY OF REPORTS FROM 1,814 PHYSICIANS (19,443 PATIENTS)

No. of Patients	Results	Percent
6,059	Excellent	31.2%
9,987	Good	51.3%
2,441	Fair	12.6%
956	Unsatisfactory	4.9%
594	Side Effects	3.1%

the rationale of

proof in practice

Because of untoward side effects, lack of patient cooperation and other factors, many products—with excellent clinical reports—fail when measured by the yardstick of day-to-day practice.

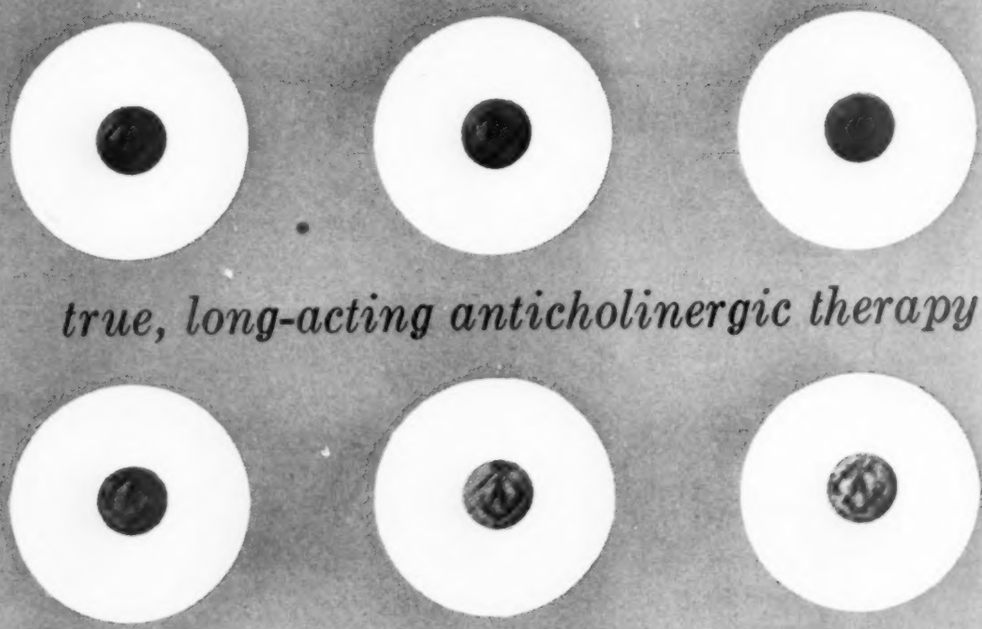
For these reasons, Unitensen (cryptenamine) was supplied to 1,814 physicians who used it to treat 19,443 hypertensive patients. Treatment was carried out while the patients engaged in their normal, everyday occupations and activities. Despite such unorthodox practices by the patients as indulging in dietary indiscretions and taking the medication other than as prescribed, the "Proof in Practice" study validates the clinical findings, and shows Unitensen is a safe, potent antihypertensive, which helps assure patient cooperation and permits office management in the great majority of patients.

Each Unitensen tablet contains: Cryptenamine (tannates) 2.0 mg. Each Unitensen-R tablet contains: Cryptenamine (tannates) 1.0 mg., Reserpine 0.1 mg.

For prescription economy, prescribe Unitensen products in 50's.

To serve your patients today—call your pharmacist for any additional information you may need to help you prescribe Unitensen or Unitensen-R.

Neisler *IRWIN, NEISLER & CO., Decatur, Illinois*



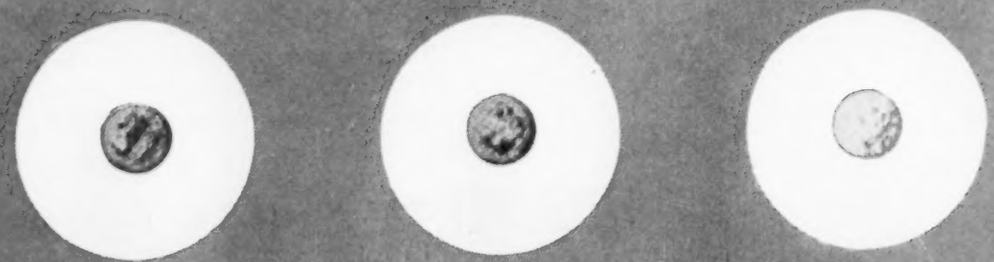
true, long-acting anticholinergic therapy

GRADUMET®

LTR

unique "metered release" of GRADUMET

assures 8 to 12 hours' continuous effect



no enteric coatings or layers

New GRADUMET TRAL has no enteric coating. Instead, the TRAL is contained in a porous, resinous matrix. On contact with gastric fluid, nearly half the TRAL dissolves and becomes available to the patient at once. The rest of the 50 mg. of anticholinergic is released slowly from the GRADUMET over the next eight to 12 hours, as gastric and intestinal fluid gradually penetrate to the innermost recesses of the GRADUMET.

no fluctuations due to patient idiosyncrasies

Since there is no enteric coating, release of the anticholinergic is not affected by changing pH of the patient's gastric acidity . . . altered rates of gastric or intestinal motility . . . or increased enzymatic activity. Relief is constant and unvarying, with no periodic "bursts" of drug activity, no sharp drop-offs of drug action in between.

A.L.®

in peptic ulcer

(*Hexocyclium Methylsulfate, Abbott*)

no anticholinergic to be wasted

The TRAL GRADUMET contains 50 mg. of the active anticholinergic . . . and the entire amount of TRAL is released from the GRADUMET in eight to 12 hours. Thus, none of the drug is wasted: Your patient gets full benefit of the dosage from GRADUMET TRAL whenever an anticholinergic effect is indicated.

New GRADUMET TRAL, 50 mg., and GRADUMET TRAL, 50 mg. with Phenobarbital, 30 mg., are supplied at pharmacies everywhere in bottles of 50 and 500. Filmtab TRAL, 25 mg., and Filmtab TRAL, 25 mg. with Phenobarbital, 15 mg., are also supplied in bottles of 100 and 1,000. Complete clinical literature—and samples—are available on request from your Abbott representative.

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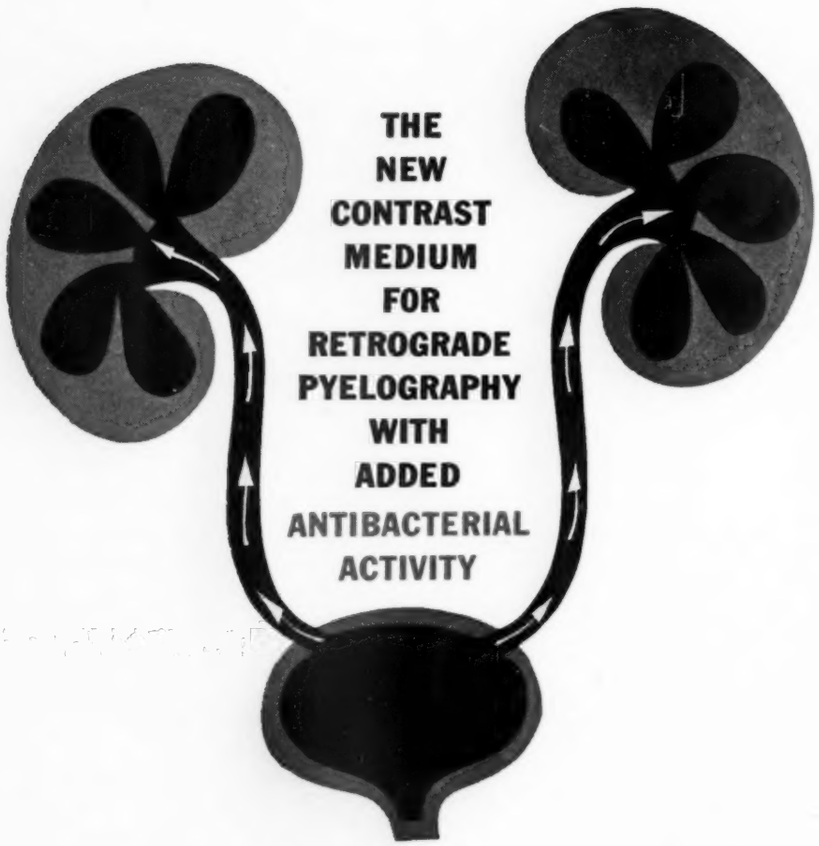

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Squibb Sodium and Methylglucamine Diatrizoates and Neomycin Sulfate

for maximum opacification when urinary tract infection is present or suspected

Retrografin provides the same excellent film quality...exceptional patient toleration...and optimal convenience in retrograde pyelography as that provided by Renografin 30%. *And,* in addition, it contains 2½% neomycin (as the sulfate) for widely effective bactericidal action in cases with proved or suspected urinary tract infection. *Supplied in 50 cc. vials*

Retrograde pyelography with either Retrografin or Renografin 30% is especially useful when poor kidney function makes other procedures impractical, or when retrograde study will provide supplemental diagnostic information.

for routine retrograde pyelography

RENOGRAFIN 30%

Squibb Sodium and Methylglucamine Diatrizoates

Its excellent local tissue tolerance and proved systemic tolerance, even in the presence of pyelo-renal backflow, make Renografin 30% the preferred agent for routine, optimal density retrograde pyelograms. *Supplied in 50 cc. vials*

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Robaxin®

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Robins

– the remarkably efficient skeletal muscle relaxant, unique in chemical formulation, and outstanding for sustained action and relative freedom from adverse side effects.

PUBLISHED REFERENCES: 1. Carpenter, E. B.: Southern Medical Journal 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Little, J. M., and Truitt, E. B., Jr.: J. Pharm. & Exper. Therap. 119:101, 1957. 4. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: J. Am. Pharm. Assn., Sci. Ed. 46:374, 1957. 5. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 6. Park, H. W.: J.A.M.A. 167:168, 1958. 7. Truitt, E. B., Jr., and Patterson, R. B., Proc. Soc. Exper. Bio. & Med. 93:422, 1957. 8. Truitt, E. B., Jr., Patterson, R. B., Morgan, A. M., and Little, J. M.: J. Pharm. & Exper. Therap. 119:189, 1957.

Supply: Tablets (white, scored), 0.5 Gm., bottles of 50 and 500.

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Ethical Pharmaceuticals of Merit since 1878

Summary of four new published clinical studies:

Robaxin Beneficial in 95.6% of Cases of Acute Skeletal Muscle Spasm[1, 2, 5, 6]

CONDITION	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
STUDY 1[1]					
Skeletal muscle spasm secondary to acute trauma	33	26	6	1	—
STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
STUDY 4[6]		"significant"			
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
TOTALS	138	104 (75.3%)	28 (20.3%)	4	2

THE JOURNAL of the American Medical Association

"In the author's clinical experience, methocarbamol has afforded greater relief of muscle spasm and pain for a longer period of time without undesirable side effects or toxic reactions than any other commonly used relaxants . . ."[2]

THE JOURNAL of the American Medical Association

"An excellent result, following methocarbamol administration, was obtained in all patients with acute skeletal muscle spasm."[5]

THE JOURNAL of the American Medical Association

"In no instance was there any significant reduction in voluntary strength or intensity of simple reflexes."[6]

Southern Medical Journal

"This study has demonstrated that methocarbamol (Robaxin) is a superior skeletal muscle relaxant in acute orthopedic conditions."[1]

UNEXCELLED ADVANTAGES . . . IN BOTH BASIC DIURETIC REGIMENS

DIAMOX*

bicarbonate-regulating diuretic

Acetazolamide Lederle

HOW DIURETICS ACT

Primarily by regulation of bicarbonate transport	DIAMOX acetazolamide
Primarily by regulation of chloride transport	mercurials chlorothiazide

1

Advantages of DIAMOX in single-drug diuresis

DIAMOX — operating through the well-understood mechanism of *bicarbonate* transport regulation—provides ample, prolonged diuresis in the great majority of patients.

DIAMOX is virtually nontoxic . . . has not caused renal or gastric irritation . . . has no pronounced effect on blood pressure. It is rapidly excreted, does not accumulate in the body, permits convenient dosage adjustment, allows unbroken sleep. Small, tasteless, easy-to-take tablets . . . usual dosage, only one a day.

- CARDIAC EDEMA
- PREMENSTRUAL TENSION
- EDEMA OF PREGNANCY
- OBESITY

2

Advantages of DIAMOX in intensive, two-drug diuresis

When intensive diuresis must be maintained, DIAMOX, alternated with an agent for regulation of *chloride* transport, has proved a regimen of choice. Through dual *bicarbonate-chloride* regulation, it produces maximal sodium-water excretion with minimal distortion of serum electrolyte patterns, greater patient comfort, lessened risk of induced drug resistance.

- ADVANCED CONGESTIVE HEART FAILURE
- REFRACTORY TOXEMIA OF PREGNANCY

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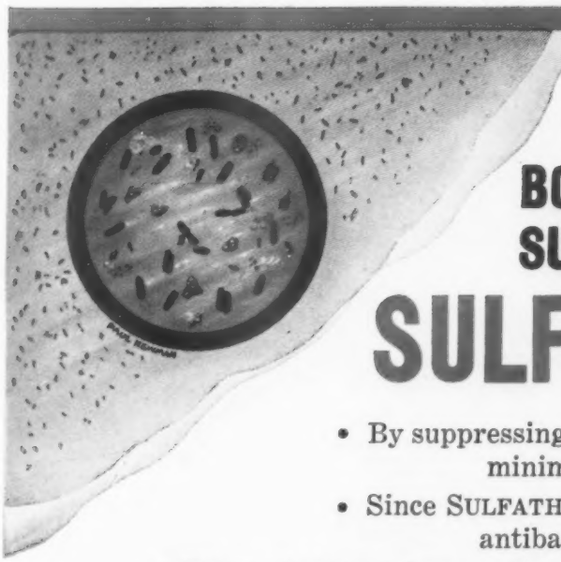

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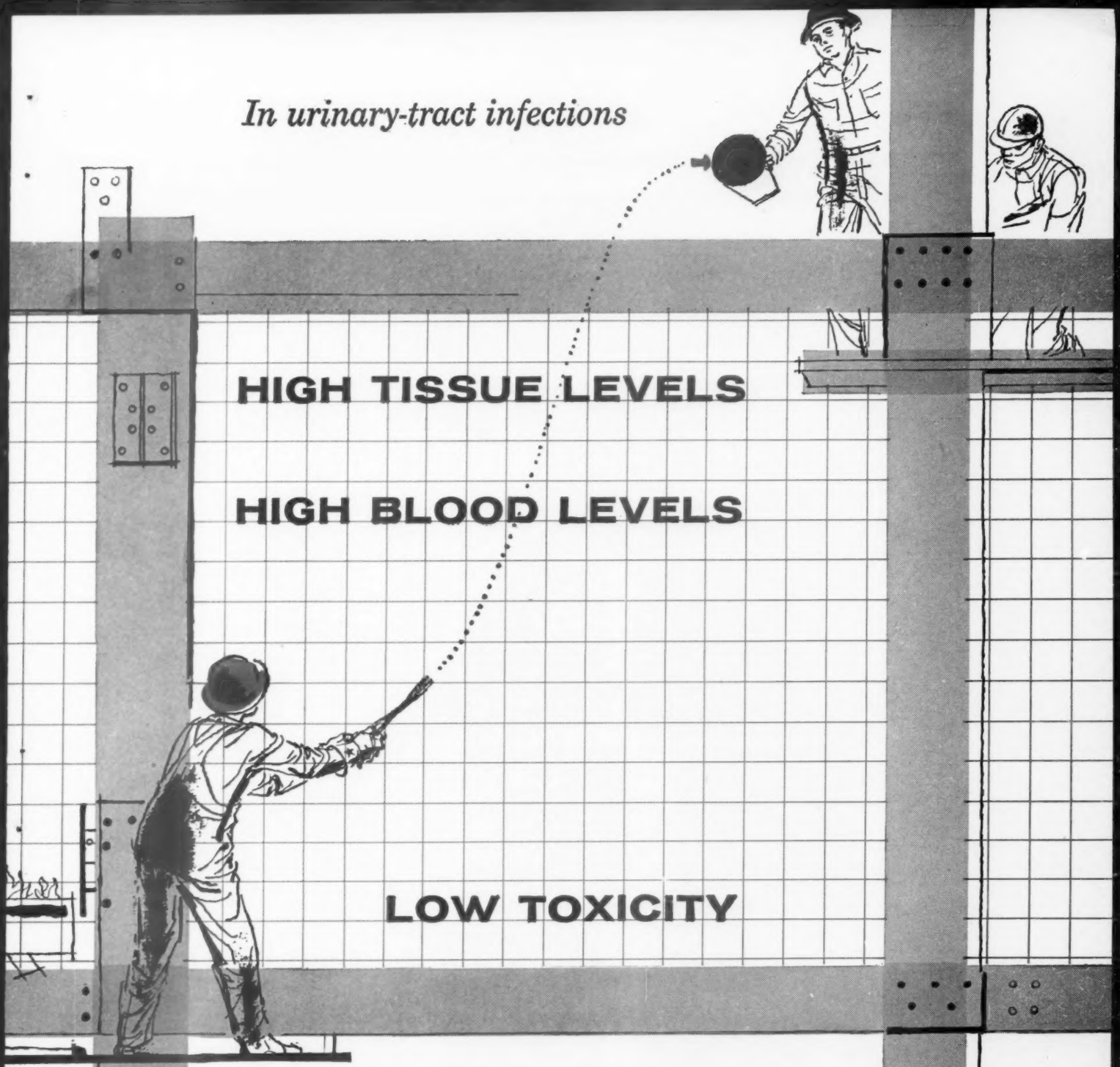

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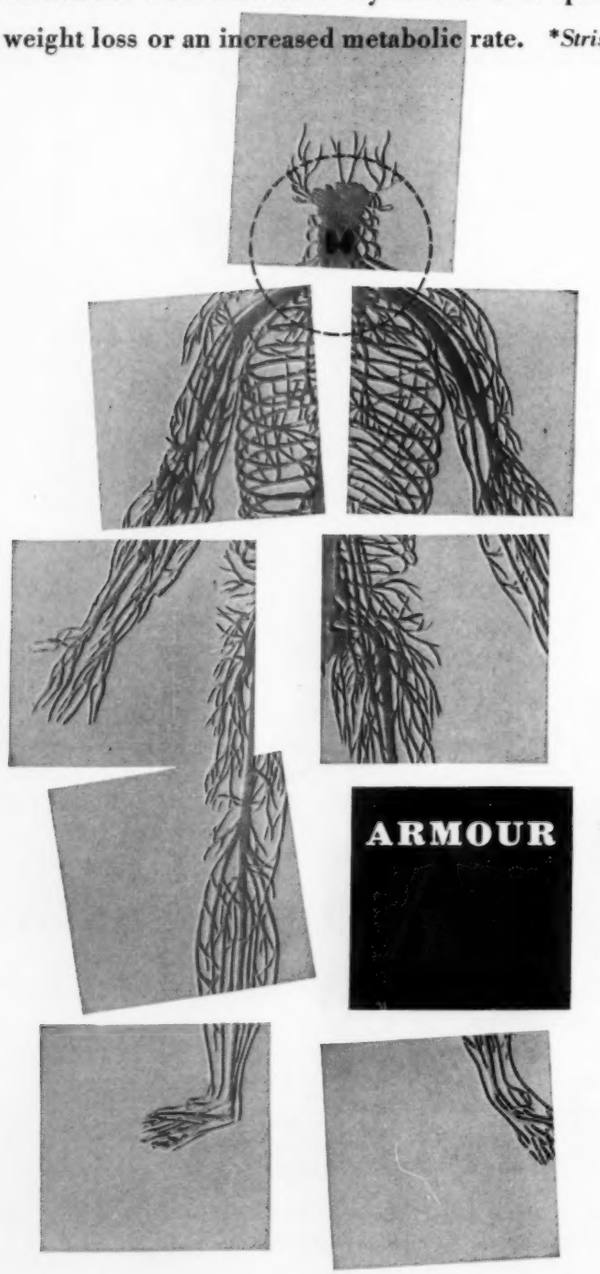

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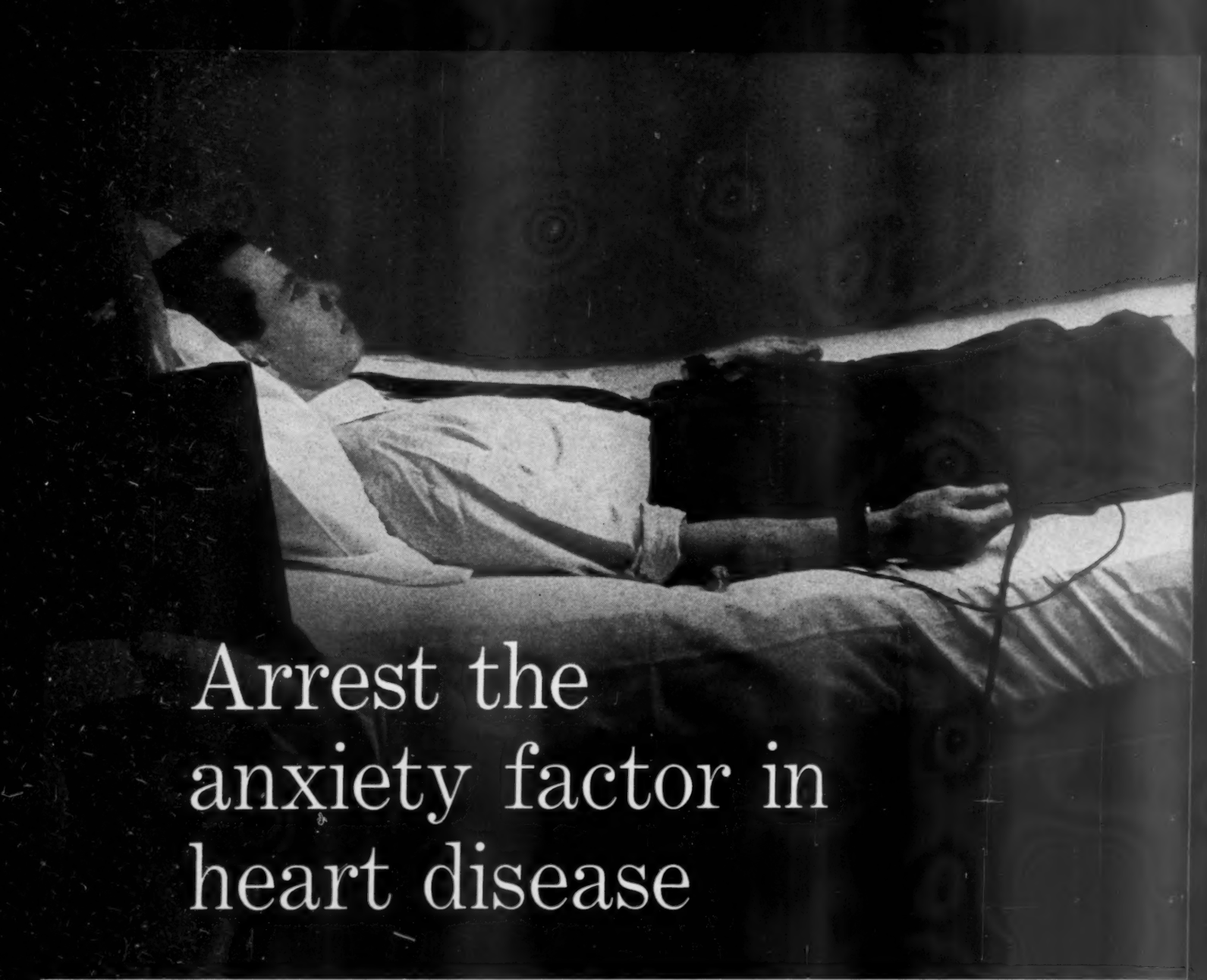

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1. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 2. Smirk, F. H., and McQueen, E. G.: Lancet 2:119, 1955. 3. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 4. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957.

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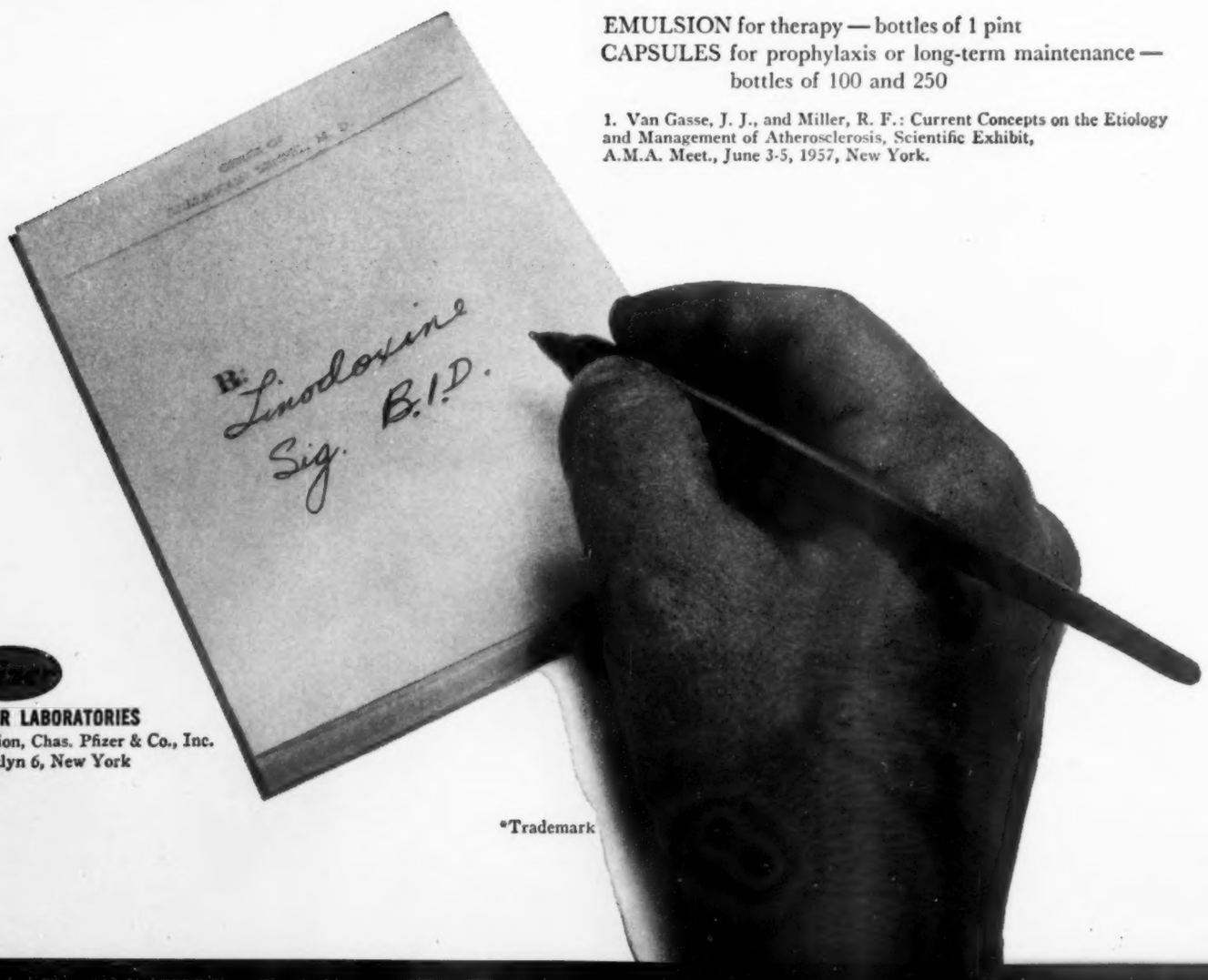
1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, A.M.A. Meet., June 3-5, 1957, New York.



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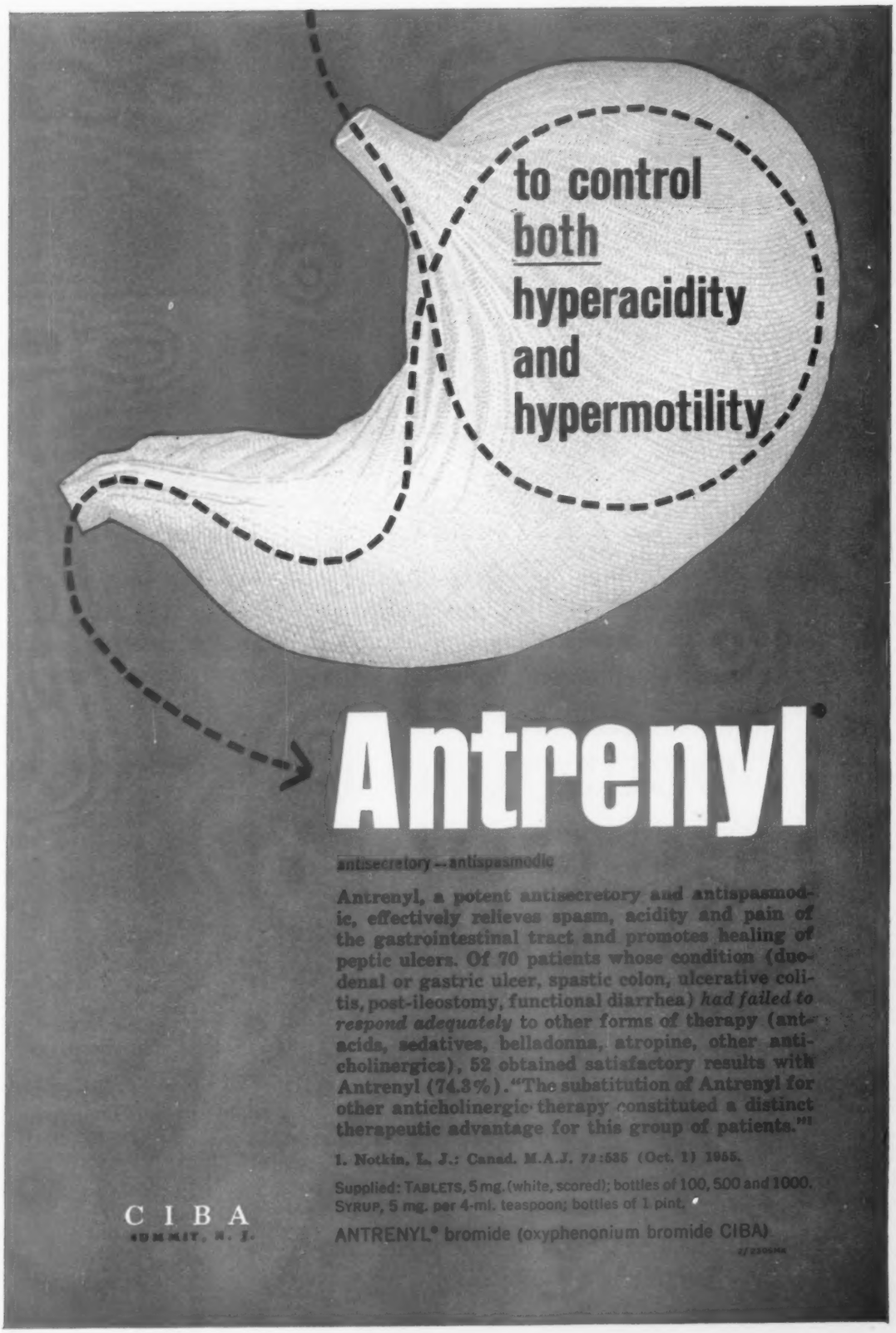
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1. Notkin, L. J.: Canad. M.A.J. 73:535 (Oct. 1) 1955.
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1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.

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1. Thomas, J. W.: Ann. Allergy *16*:128, 1958

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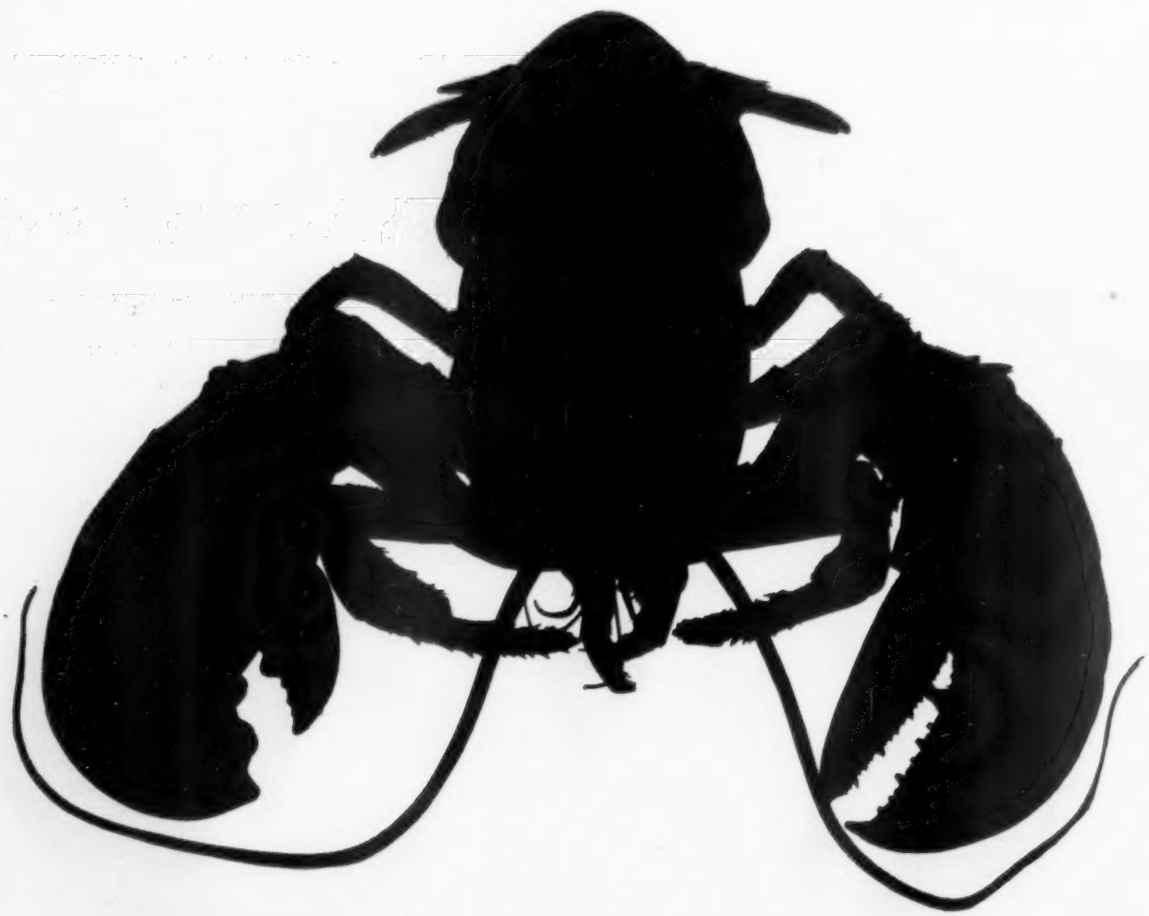

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2. MAC LAREN, W. R. ET AL.: ANN. ALLERGY 13:307-312 (MAY-JUNE) 1955.

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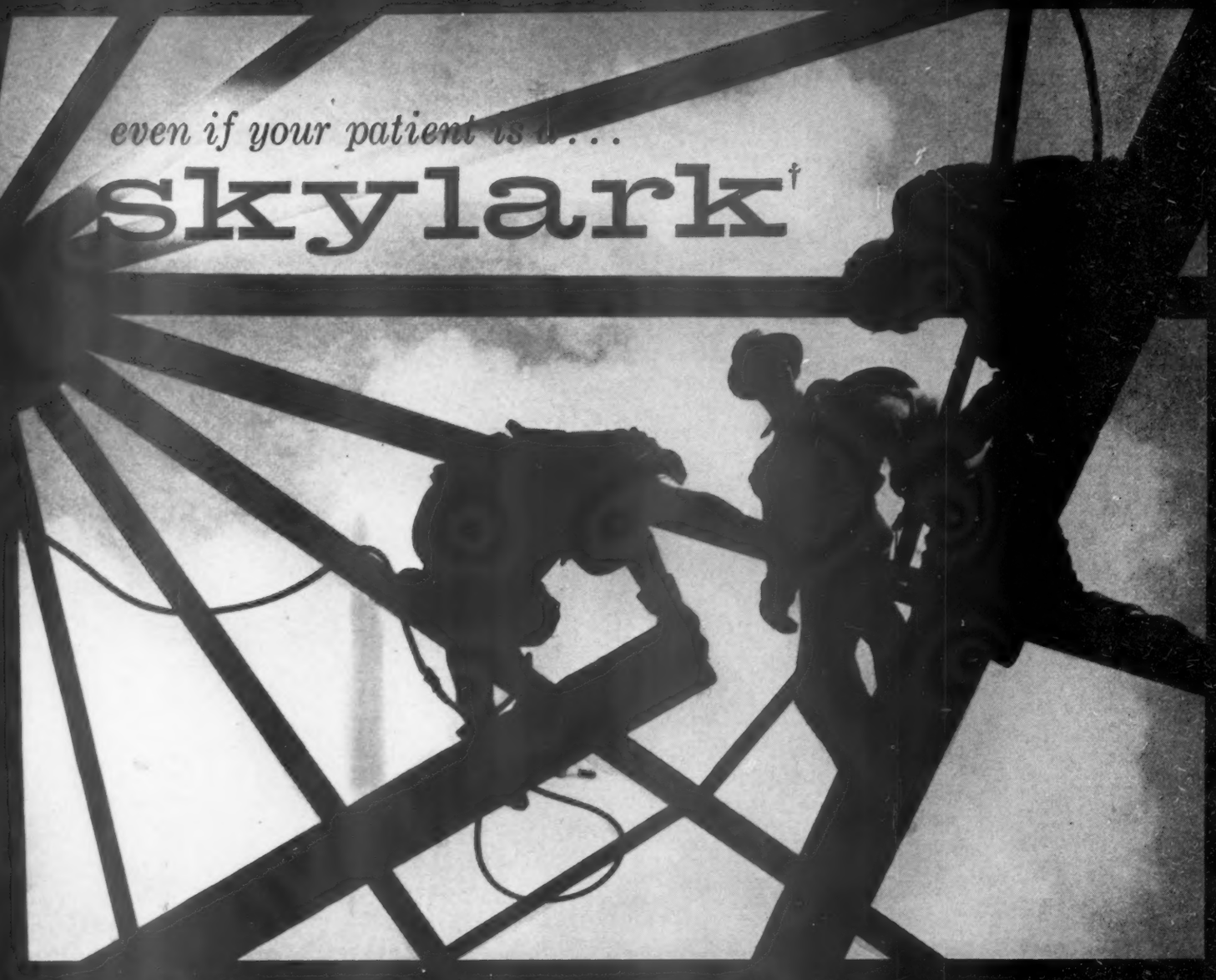

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...AND FREQUENTLY COMPLICATED

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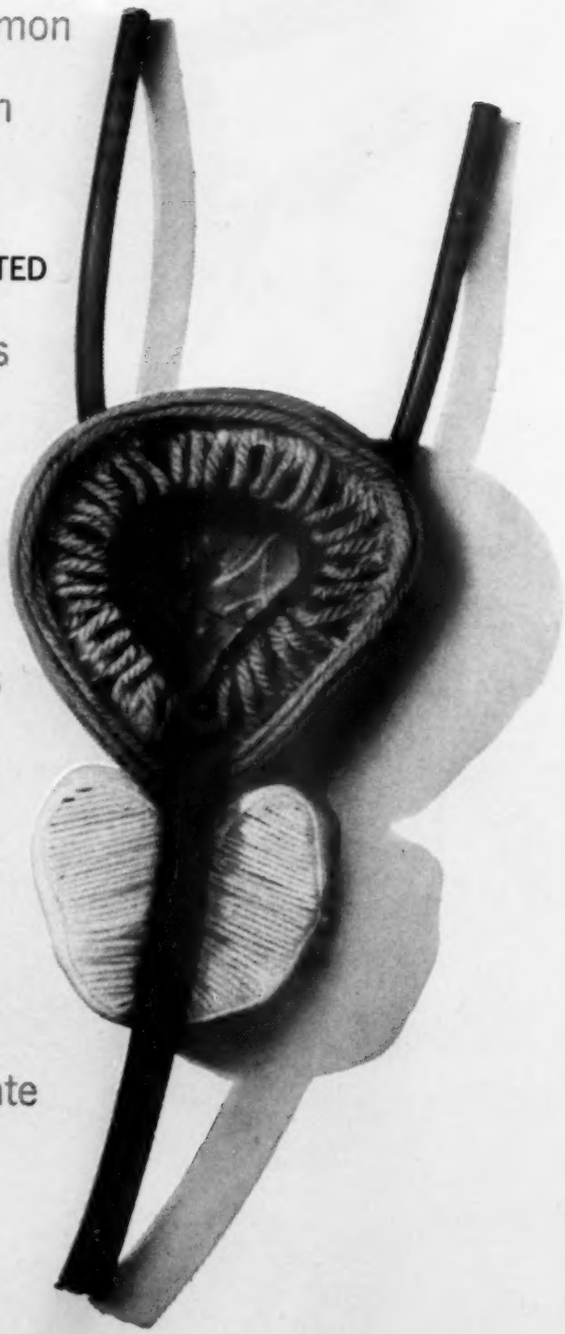

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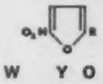

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1. Shalowitz, M.: Geriatrics 11:312, 1956. 2. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957. 3. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind. 4. Strub, I. H.: To be published. 5. Individual Case Reports to Medical Dept., Pfizer Laboratories.

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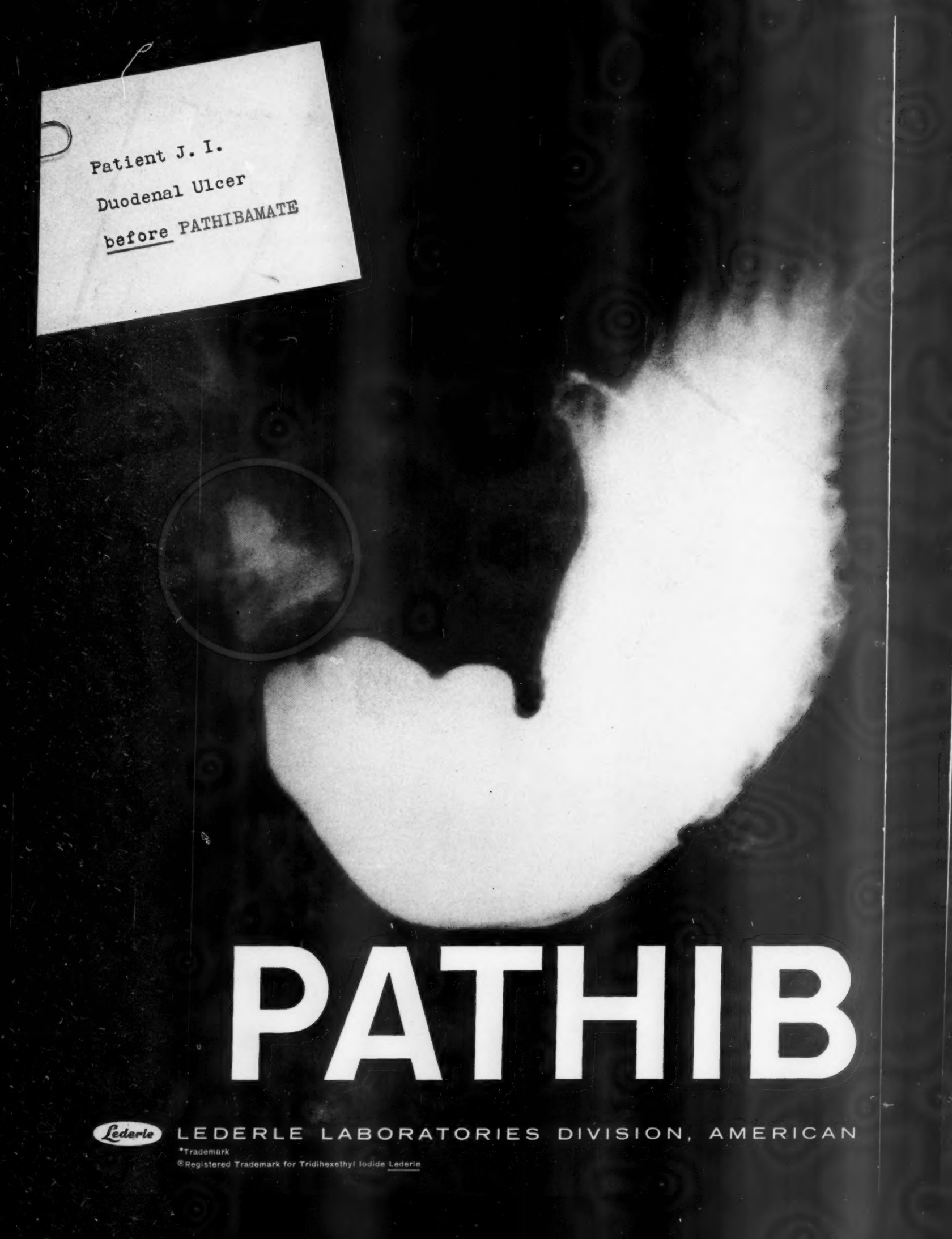

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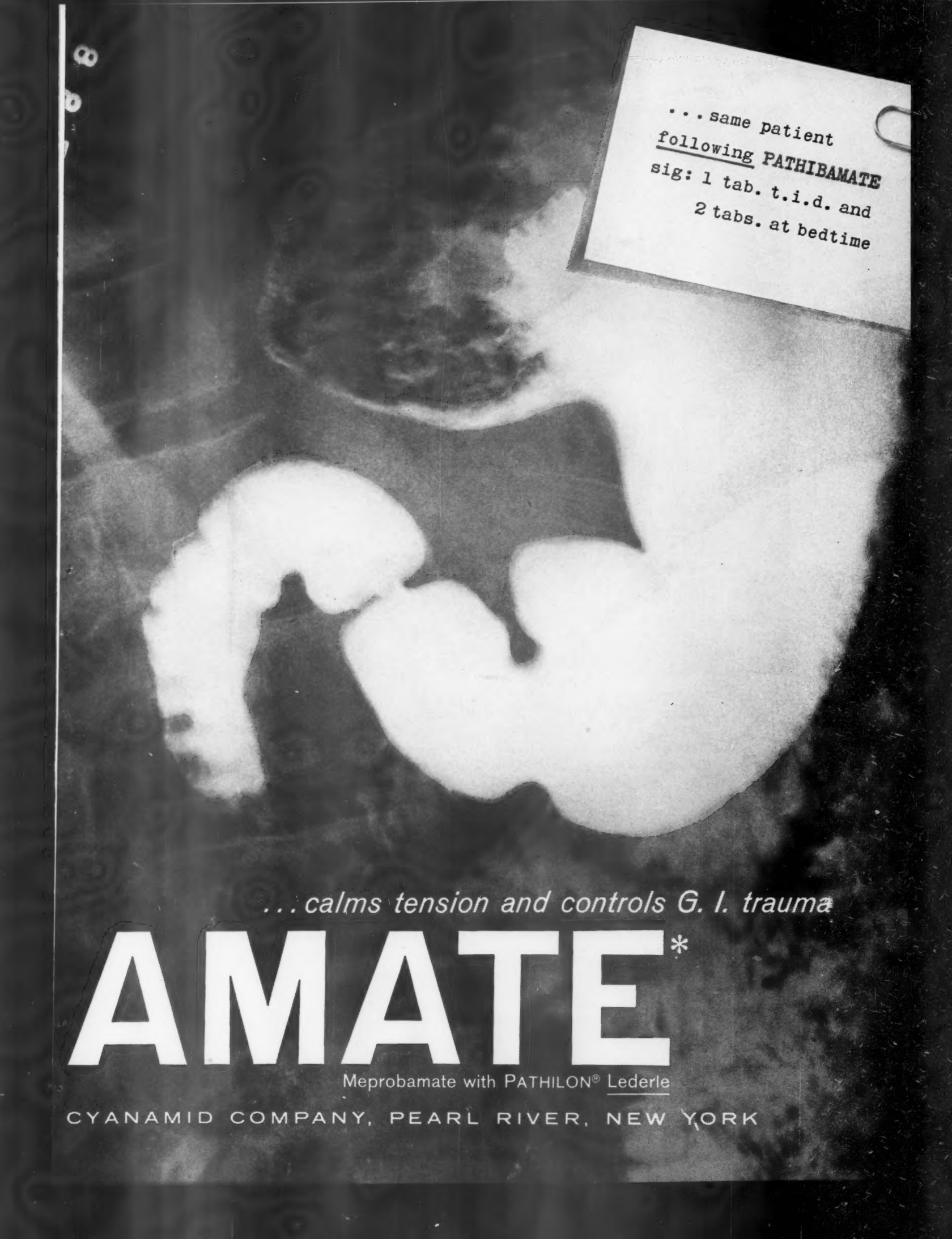

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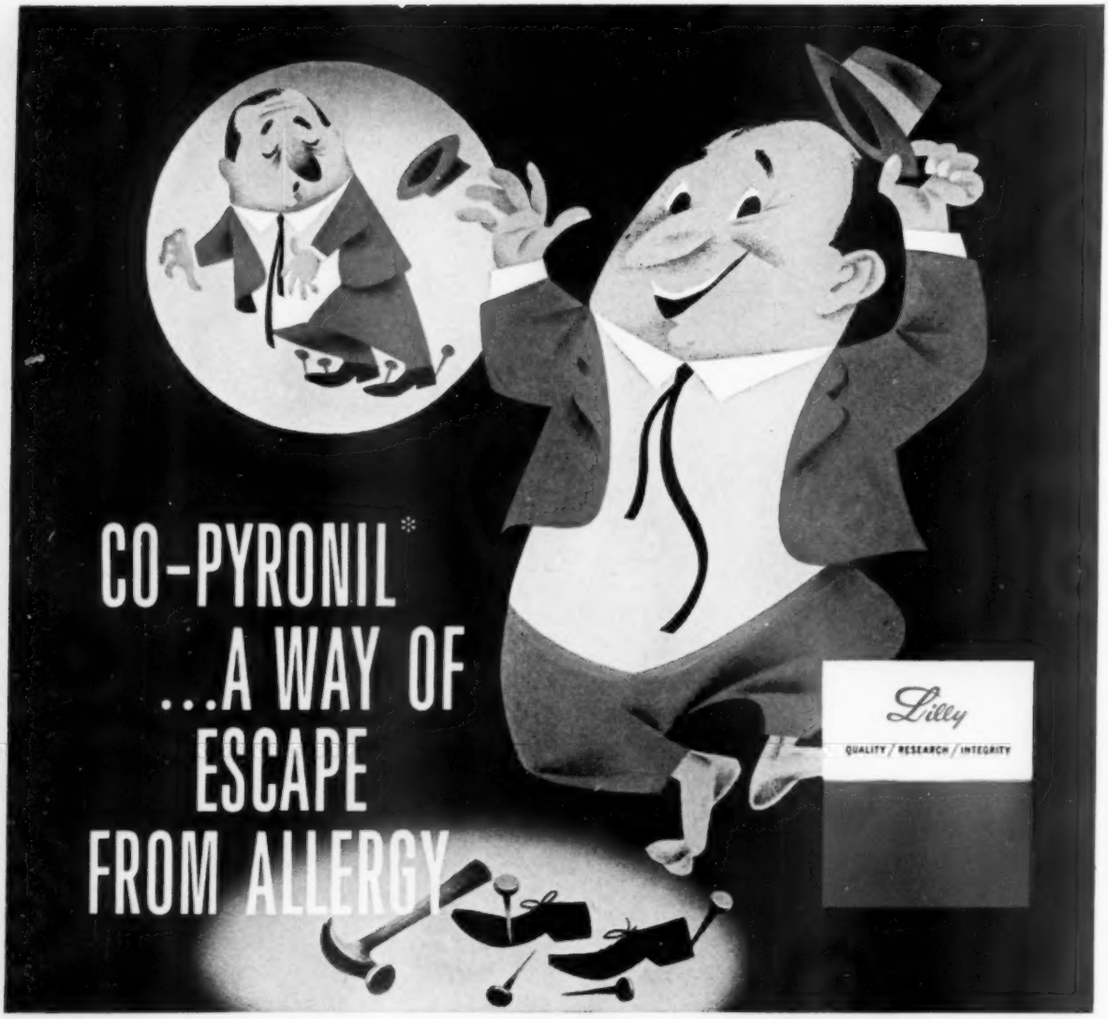

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Editorial

Insulin Antagonists, Insulin Antibodies and Insulin Resistance

THE recent medical literature abounds in reports of serum factors observed to oppose the action of insulin. Unfortunately, the multiplicity of technics employed in the detection of such insulin "antagonists" * has led to some confusion regarding the kinship of these various factors and the nature of their opposition to insulin. The confusion is compounded when one group of workers fails to encounter an antagonist previously reported by others under essentially similar conditions while uncovering a new antagonist not observed by the earlier investigators.

One ready distinction can be made among the various anti-insulin factors, i.e., whereas the antibody nature of certain insulin antagonists has been established, others are clearly to be differentiated from antibodies in that they are demonstrable in the absence of previous administration of exogenous insulin. The antibody antagonists are obviously not to be indicted in the etiology of diabetes mellitus. The possibility that one or another of the non-antibody antagonists is involved in the causation of diabetes has been suggested on occasion, but remains unproved.

Probably the most intensively studied insulin antagonist is an enzyme system ("insulinase") [*1*] which is capable of degrading insulin proteolytically. Although the specificity of the system(s) involved may remain open to some question, there is little doubt that insulinase is responsible for the very short life span of insulin *in vivo*; in man, half of the circulating insulin is degraded in about thirty-five minutes [*2*]. The possibility that excessive activity of insulinase or deficiency of a normally occurring insulinase-inhibitor might be of etiologic significance in diabetes has been suggested by Mirsky [*3*]. However, tracer experiments with I^{131}-labeled insulin have failed to show an abnormally rapid rate of insulin degradation in untreated human diabetic subjects [*2*].

While liver, kidney and muscle possess active insulinase systems, insulin degradation in plasma normally proceeds only at a very slow rate [*2*]. Nevertheless, on occasion, certain plasma samples (especially after aging for several weeks at 4°C.) are capable of rapidly destroying rather large amounts of iodinated insulin [*4*]. The enzymic nature of this destruction has not been demonstrated but the different insulin degrading

* "Antagonist" is used only in the very general sense to indicate an inhibitory-modifying effect on the action of insulin in any specific test system.

[1] MIRSKY, I. A. Insulinase, insulinase-inhibitors, and diabetes mellitus. *Rec. Prog. Hormone Research*, 13: 429, 1957.

[2] BERSON, S. A., YALOW, R. S., BAUMAN, A., ROTHSCHILD, M. A. and NEWERLY, K. Insulin-I^{131} metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin-treated subjects. *J. Clin. Investigation*, 35: 170, 1956.

[3] MIRSKY, I. A. The etiology of diabetes mellitus in man. *Rec. Prog. Hormone Research*, 7: 437, 1952.

[4] BERSON, S. A. and YALOW, R. S. Unpublished observations.

capacities of serums have been found not to be related to the presence or absence of diabetes. The unpredictable presence of such factors (possibly simple reducing substances) might account for certain inconsistencies in experimental results.

Technics used commonly for the assay of insulin activity or for detection of insulin inhibitors are based on the earlier observation of Gemmill [*5*] that the uptake of glucose by isolated rat diaphragm is augmented by insulin. The glucose uptake may be estimated from the difference in glucose concentration of the medium before and after incubation; alternatively, the increase in glycogen content of the diaphragm induced by brief exposure to insulin (0.1 U./ml.) prior to incubation in glucose soluton may be determined (Stadie technic) [*6*]. Many replicate determinations are required in the former method since the decrement in glucose concentration of the medium during the experiment frequently amounts only to about 10 to 20 per cent of the initial concentration and small errors in determination of glucose produce large relative differences in calculated glucose uptakes.

Bornstein and Park [*7*] observed that glucose uptake by isolated rat diaphragm was about twice as great when incubated in serum obtained from normal fasting rats as when incubated in buffer solution without protein. The uptake of glucose by diaphragms incubated in the serum of alloxan-diabetic rats was about 25 per cent lower than in the serum of normal rats. The possibility that this difference was due to insulin present in the serum of normal rats was considered unlikely since adrenalectomy or hypophysectomy of the diabetic serum donors restored glucose uptake to normal. It was therefore concluded that the serum of diabetic animals inhibited glucose uptake. However, since addition of insulin increased the glucose uptake to the same level whether the serum donors were normal or diabetic animals, no evidence for insulin antagonism per se was found, although the high concentration of insulin used (0.1 U./ml.) might have obscured such antagonism even if present. The inhibitor was recovered in the lipoprotein fraction of the serum [*8*] and was destroyed by repeated freezing and thawing. Corroboration of these results has been reported [*9*].

Employing a similar test system, Vallance-Owen and Lukens [*10*] have observed that the serum of pancreatectomized cats inhibits the increase in glucose uptake stimulated by the addition of .001 U. insulin/ml. but does not alter glucose uptake in the absence of added insulin. The inhibitory factor did not develop when hypophysectomy or adrenalectomy was performed together with the pancreatectomy. Furthermore, treatment of pancreatectomized-adrenalectomized animals with cortisone or hydrocortisone for three to four days resulted in the appearance of the inhibitory factor. The insulin antagonist was stable to repeated freezing and thawing, and was recovered with the serum globulins salted out by saturated sodium chloride.

Thus two apparently different factors, one a lipoprotein which inhibits glucose uptake in the absence of insulin, the other a non-lipoprotein fraction which acts as an insulin antagonist, are reported to develop in depancreatized animals under conditions characterized by the presence of pituitary and adrenocortical hormones. We should not omit notice of the fact that Vallance-Owen and Lukens [*10*], working with cats, failed to observe either the augmentation of glucose uptake (above that from buffer solutions) by serum from depancreatized-hypophysectomized or depancreatized-adrenalectomized animals, or the inhibition by serum of depancreatized animals in the absence of insulin, reported earlier in rats by Bornstein and Park [*7*]. Furthermore, Groen et al. [*11*], using similar technics, had found no insulin antagonism in the serums of

[5] Gemmill, C. L. Effects of glucose and of insulin on metabolism of isolated diaphragm of the rat. *Bull. Johns Hopkins Hosp.*, 68: 329, 1941.

[6] Stadie, W. C., Haugaard, N., Marsh, J. B. and Hills, A. G. The chemical combination of insulin with muscle (diaphragm) of normal rats. *Am. J. M. Sc.*, 218: 265, 1949.

[7] Bornstein, J. and Park, C. R. Inhibition of glucose uptake by the serum of diabetic rats. *J. Biol. Chem.*, 205: 503, 1953.

[8] Bornstein, J. Insulin-reversible inhibition of glucose utilization by serum lipoprotein fractions. *J. Biol. Chem.*, 205: 513, 1953.

[9] Hendley, E. D., Bregman, E. and Krahl, M. E. Inhibition of muscle glucose upake by diabetic rat sera of varying glucose and lipoprotein content. *J. Biol. Chem.*, 226: 459, 1957.

[10] Vallance-Owen, J. and Lukens, F. D. W. Studies on insulin antagonism in plasma. *Endocrinology*, 60: 625, 1957.

[11] Groen, J., Kamminga, C. E., Willebrands, A. F. and Blickman, J. R. Evidence for the presence of insulin in blood serum. A method for an approximate determination of the insulin content of blood. *J. Clin. Investigation*, 31: 97, 1952.

depancreatized dogs. Whether the species differences alone are accountable for these discrepancies remains unknown.

Earlier, Vallance-Owen and co-workers [*12*] had reported an insulin-inhibitory factor in the serum of poorly controlled (but not ketotic) human diabetic subjects requiring insulin. In two of these patients studied subsequently the inhibitory factor had disappeared after control of the hyperglycemia had been effected. It was stated subsequently [*10*] that the inhibitor could be demonstrated in subjects previously untreated with insulin and was therefore not attributable to antibodies.

Employing the Stadie technic [*6*], Field and Stetten [*13*] have observed an insulin antagonist to be present in the serum of five of seven patients with diabetic acidosis. One of these had never been treated previously with insulin and the antagonist was equally effective against human or beef-pork insulin [*14*]. These workers found that the increment in glycogen synthesis was markedly reduced or abolished whether the diaphragm was exposed to the inhibitory serum before, after, or at the same time as exposure to insulin. Serum from normal subjects had no significant effect on glycogen accumulation under these conditions. Electrophoretic separation technics revealed the antagonist to be present primarily in the α globulin component [*15*]; the lipoproteins showed no inhibitory activity. The inhibitor was destroyed by chymotrypsin but not by trypsin [*14*], was stable to repeated freezing and thawing, and was destroyed by heating at 100°C. [*15*]. In two cases the serum showed loss of inhibitory activity six and nine hours respectively following initiation of insulin therapy [*13*]. The antagonist was not demonstrable in the serums of two patients with diabetes and acromegaly showing resistance to insulin or in the serum of one of these patients given a prolonged infusion of ACTH.

[12] Vallance-Owen, J., Hurlock, B. and Please, N. W. Plasma-insulin activity in diabetes mellitus measured by the rat diaphragm technique. *Lancet*, 2: 583, 1955.

[13] Field, J. B. and Stetten, D., Jr. Humoral insulin antagonism associated with diabetic acidosis. *Am. J. Med.*, 21: 339, 1956.

[14] Field, J. B., Tietze, F. and Stetten, D., Jr. Further characterization of an insulin antagonist in the serum of patients in diabetic acidosis. *J. Clin. Investigation*, 36: 1588, 1957.

[15] Field, J. B. and Stetten, D., Jr. Studies on humoral antagonists in diabetic acidosis. *Diabetes*, 5: 391, 1956.

Using the same technic, Marsh and Haugaard [*16*] had earlier reported insulin inhibition by serums from normal patients and mild diabetic subjects but much more marked inhibition by serums from three severely insulin-resistant patients. Since the serum had to be present at the time of exposure of the diaphragm to insulin, it was concluded that the inhibitory substances combined with or inactivated the insulin and it was suggested that an antigen-antibody combination might have taken place. Although these authors did not fractionate the inhibitory serum, the absence of insulin antagonism when the diaphragm was exposed first to serum and then to insulin indicates that the inhibitory factor of Field and Stetten was not present. However, the presence or absence of acidosis was not noted. Groen et al. [*11*], by measuring glucose uptake in the diaphragm, had failed previously to find evidence of insulin antagonism in the serums of patients with diabetic coma.

Baird and Bornstein [*17*] have recently extracted plasma insulin, using a mixture of organic solvents, and claim to have demonstrated inhibiting factors in the serums of normal subjects as well as of insulin-resistant and non-resistant diabetic patients. A factor which resisted inactivation in the extraction process inhibited glucose uptake by the isolated rat diaphragm in the absence of added insulin and (in one experiment with serum from an insulin-resistant patient) protected mice against hypoglycemic convulsions induced by insulin. The authors concluded that this stable factor was probably the same as that described by Field and Stetten. However, since the stable factor was found to be present in the serum of all of seven normal subjects and in all of eight controlled diabetics but was absent from the serum of four (one insulin-resistant) of seven diabetic patients in coma, it is difficult on this basis to resolve this conclusion with the findings of Field and Stetten or to attribute importance to this factor in the development of insulin resistance. The presence of a labile insulin antagonist was inferred from the observation that whereas insulin could not be demonstrated in crude plasma of insulin-resistant

[16] Marsh, J. B. and Haugaard, N. The effect of serum from insulin-resistant cases on the combination of insulin with the rat diaphragm. *J. Clin. Investigation*, 31: 107, 1952.

[17] Baird, C. W. and Bornstein, J. Plasma-insulin and insulin resistance. *Lancet*, 1: 1111, 1957.

patients, extracts of these plasmas revealed insulin activity by the diaphragm technic. However, the amount of insulin which could be extracted from serums of patients who had received as much as 8,000 units of insulin in the preceding twenty-four hours was not greater than that extracted from other serums. It seems quite possible that much of the insulin administered to the resistant subjects was bound to insulin-binding antibody (to be described) and thus resisted extraction, and, moreover, that such antibody was responsible for the insulin resistance.

In summary, it may be said that while individual laboratories have reported reproducible results with the particular insulin antagonist of their interest using *in vitro* diaphragm technics, there has not as yet been sufficient agreement between independent laboratories even when experimental conditions have been apparently similar. At least part of the difficulty may be attributed to the marked variability in sensitivity of the methods even when technic is rigidly standardized [*18*].

Except for the studies of Haugaard and Marsh [*17*], no distinct correlation has been demonstrated between insulin resistance and the presence of the insulin antagonists described. On the other hand, the role of antibodies in clinical insulin resistance has been documented (albeit only occasionally) in cases in which insulin-neutralizing or other antibodies were demonstrable [*19–23*], particularly by the mouse convulsion test. However, because of the paucity of such cases and the difficulty experienced in immunizing animals to insulin (cf. [*20*]), the hormone was generally regarded as being only poorly antigenic. Nevertheless, successful immunization in animals has been reported [*24–26*]. Furthermore, it has been demonstrated recently, by sensitive electrophoretic and ultracentrifugal technics employing insulin-I^{131}, that in almost all human subjects (diabetic or nondiabetic) receiving exogenous insulin, antibodies capable of binding insulin *in vivo* and *in vitro* soon appear [*2*]. The presence of insulin-binding antibodies in insulin-treated, non-resistant subjects has also been observed by others using similar electrophoretic methods [*27–29*], and the precipitation by rabbit antihuman globulin of insulin-I^{131} added to the serums of such subjects has been reported [*30*]. The failure of some workers to detect insulin-binding antibodies by paper electrophoresis except in serums of insulin-resistant patients [*31*] may have been due to a lack of sufficient sensitivity in technic.

The difference between insulin resistance and non-resistance in insulin-treated patients appears to be primarily a quantitative one. The total insulin-binding capacity of serums from non-resistant, treated subjects is rarely greater than 10 units/L. plasma [*2*] whereas binding capacities of as much as 500 units/L. [*32,33*] and greater [*4*] have been observed in serums from insulin-resistant patients. Insulin bound to antibody is not immediately available to the cells and insulin requirements in such cases must be expected to increase. Not only is there an acute need for large amounts of insulin at times

[18] Willebrands, A. F. and Groen, J. Determination of serum insulin by the rat diaphragm method. Further observations in diabetic and nondiabetic subjects and in hyperinsulinism. *Diabetes*, 5: 378, 1956.

[19] Lowell, F. C. Evidence for the existence of two antibodies for crystalline insulin. *Proc. Soc. Exper. Biol. & Med.*, 50: 167, 1942.

[20] Lerman, J. Insulin resistance: the role of immunity in its production. *Am. J. M. Sc.*, 207: 354, 1944.

[21] DeFillipis, V. and Iannaccone, A. Insulin-neutralizing activity of gamma-globulins derived from the serum of an insulin-resistant patient. *Lancet*, 1: 1191, 1952.

[22] Sehon, A. H., Kaye, M., McGarry, E. and Rose, B. Localization of an insulin-neutralizing factor by zone electrophoresis in a serum of an insulin-resistant patient. *J. Lab. & Clin. Med.*, 45: 765, 1955.

[23] Colwell, A. R. and Weiger, R. W. Inhibition of insulin action by serum gamma globulin. *J. Lab. & Clin. Med.*, 47: 844, 1956.

[24] Wasserman, P., Broh-Kahn, R. H. and Mirsky, I. A. Antigenic property of insulin. *J. Immunol.*, 38: 213, 1940.

[25] Moloney, P. J. and Coval, M. Antigenicity of insulin: diabetes induced by specific antibodies. *Biochem. J.*, 59: 179, 1955.

[26] Arquilla, E. R. and Stavitsky, A. B. The production and identification of antibodies to insulin and their use in assaying insulin. *J. Clin. Investigation*, 35: 458, 1956.

[27] Weiger, R. W. and Colwell, A. R. The inhibition of insulin action by serum gamma globulin. (Abstract.) *Clin. Research Proc.*, 4: 123, 1956.

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[29] Grodsky, G. M. and Forsham, P. H. Binding mechanism for insulin in "insulin-resistant" sera. *Fed. Proc.*, 17: 234, 1958.

[30] Skom, J. H. and Talmage, D. W. Nonprecipitating insulin-binding antibodies. (Abstract.) *J. Lab. & Clin. Med.*, 48: 943, 1956.

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[32] Berson, S. A. and Yalow, R. S. Kinetics of reaction between insulin and insulin-binding antibody. (Abstract.) *J. Clin. Investigation*, 36: 873, 1957.

[33] Berson, S. A. and Yalow, R. S. Studies with insulin-binding antibody. *Diabetes*, 6: 402, 1957.

when there is an abrupt increase in antibody concentration but also the normal turnover of antibody may be responsible for continued high insulin requirements. Owing to its degradation together with antibody, a large fraction of the bound insulin may never become available to the tissues. This alone could account for the wastage of several hundred units of insulin daily in subjects with high binding capacities. The possibility that other insulin antagonists contribute to the insulin resistance manifested clinically cannot be excluded. However, the quantitative agreement between insulin-binding capacity of the serum and insulin requirements in patients with insulin resistance [*4*] suggests that insulin-binding antibody may well be the important factor. Moreover, certain characteristic clinical phenomena associated with insulin resistance appear to be compatible with an insulin-binding process *in vivo*. It is not uncommonly observed that an insulin-resistant patient requiring relatively enormous doses of insulin (of the order of several thousand units in a day or two) to control ketosis during an acute episode may, for several days following, experience recurrent hypoglycemic reactions in the absence of further insulin therapy. This picture is most readily explained by slow release of the insulin "trapped" in circulating insulin-antibody complexes. Dissociation of these complexes has been observed *in vitro* [*32–34*] and can account quantitatively for the clinical pattern observed.

The presence of insulin-binding antibody as demonstrated by zone electrophoresis has been shown to be correlated with the retention of insulin-I^{131} in the circulation of insulin-treated subjects [*2*], and binding of insulin by plasma and ethanol-separated plasma protein fractions has been demonstrated to be responsible for the protection of insulin against liver insulinase *in vitro* [*35*]. Further, the protection of mice against the hypoglycemic effects of insulin administered together with plasma from insulin-treated subjects was found, by Welsh et al. [*36*], to be correlated with marked retention of insulin-I^{131} in the circulation of the plasma donors. Insulin-binding antibody was also present in high concentration in serums from insulin-resistant patients previously observed to possess insulin-neutralizing antibodies [*31*]. These observations suggest strongly that insulin-binding and insulin-neutralizing antibodies are identical. Although insulin-neutralizing antibodies have been reported to migrate with γ globulins separated by salt fractionation of antiserums [*21–23*], whereas insulin-binding antibodies were found to accompany the inter β-γ proteins on ethanol fractionation [*37*], the apparent discrepancy may be explained by the likelihood that inter β-γ globulins are salted out together with γ globulins. By electrophoresis convection, Loveless and Cann [*38*] have shown skin-sensitizing antibody to migrate with the β globulins, and blocking antibody to be present in the slow as well as the fast γ globulin fractions. Lowell [*19*] had earlier reported that insulin-neutralizing and insulin-sensitizing antibodies are distinguishable. Since it might be anticipated that the "insulin-binding globulin" detected by zone electrophoresis would possess "blocking" activity as well, it is not possible at the present time to conclude definitely whether the various antibodies described differ uniquely or are in fact identical. That they are responsible for diverse manifestations of insulin antagonism appears to be indisputable.

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Clinical Studies

Role of Hageman Factor in the Initiation of Clotting by Glass*

Evidence that Glass Frees Hageman Factor from Inhibition

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BLOOD as it circulates through the vascular tree is fluid, yet clots after only a brief interval when it is removed from the body and transferred to glass containers. This enigma, perhaps a clue to the genesis of intravascular thrombi, remains unresolved.

Bordet and Gengou [*1*] found that the clot-promoting effect of glass could be demonstrated even after the bulk of the blood cells had been removed, an observation since confirmed by Lozner [*2*], Conley and his associates [*3*] and others. Shafrir and de Vries [*4*] and Margolis [*5,6*] reported recently that the clot-promoting effect of glass was demonstrable in plasma which had been adsorbed with barium sulfate or aluminum hydroxide and heated at 56°C. for thirty minutes. Plasma treated in this manner is devoid of all described clotting factors except plasma thromboplastin antecedent (PTA) [*7*] and Hageman factor [*8*]. The present study confirms and extends these findings. The clot-promoting effect of glass was observed in plasmas obtained from patients with a variety of coagulative abnormalities. However, the clot-promoting effect could not be demonstrated in plasma deficient in Hageman factor. Presumably the presence of Hageman factor was required to demonstrate the clot-promoting effect of glass.

There are several possible explanations for the action of glass. Fiala [*9*], experimenting with horse plasma, claimed to have identified an inhibitory substance which was removed upon contact with glass or barium carbonate. According to this view, plasma, thus freed from inhibition, would clot. Evidence will be presented compatible with the concept that glass exerts its clot-promoting effect by releasing Hageman factor from inhibition. Plasma obtained from patients or animals deficient in Hageman factor impeded the clot-promoting effect of glass upon normal plasma. However, once glass had been allowed to exert its effect upon normal plasma, the addition of plasma deficient in Hageman factor did not appreciably impede clotting. These experiments are consistent with the hypothesis that the fluidity of blood within blood vessels is maintained by the presence of inhibitory substances directed against Hageman factor. Exposure of blood to glass removes this inhibition. The uninhibited Hageman factor then initiates or promotes clotting.

Margolis [*5,6*] also reported that the accelerator which appeared when plasma was treated with glass was labile; its activity appeared to be destroyed by some agent in plasma. Data will be presented which indicate that plasma contains an enzyme which inactivates Hageman factor. The implication of this observation will be discussed.

METHODS

Nomenclature. Hageman trait describes an asymptomatic familial syndrome in which the subject's plasma lacks Hageman factor, a clot-promoting factor present in normal barium sulfate-adsorbed, heated plasma or serum. Plasma deficient in Hageman factor will be referred to as Hageman-deficient plasma.

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Materials. Blood was drawn from the antecubital veins of human subjects and from the hearts of ducks, using No. 18 gauge needles coated with tris-(2-hydroxyethyl)dodecyl-ammonium chloride (monocote,® Armour) and glass syringes coated with silicone (G.E. Dri-Film). Oxalated and citrated plasma were prepared by mixing nine parts of blood with one part of 0.1M sodium oxalate or 0.13M trisodium citrate dihydrate and removing the cells by centrifugation at 2,000 G for fifteen minutes in an International SB Size 1 centrifuge at 4°C. Platelet-deficient oxalated or citrated plasma was prepared by recentrifuging plasma twice at 27,000 G for ten minutes in an International High Speed Centrifuge at 4°C. Such plasma usually contained less than 100 platelets per $mm.^3$ by direct count, using phase microscopy [*10*]. The plasma was kept in silicone-coated tubes except as noted. It was refrigerated in ice water and used within a few hours, or stored at −25°C. for as long as two months until used.

Plasma from patients thought to be deficient in Stuart factor [*11*] and plasma thromboplastin antecedent [*7*] were obtained through the kindness of Dr. J. B. Graham (Chapel Hill, North Carolina) and Dr. R. L. Rosenthal (New York, New York) respectively. These plasmas were lyophilized in glass containers and were reconstituted by the addition of water.

Barium sulfate-adsorbed, heated plasma was prepared by adding 100 mg. of powdered barium sulfate (Baker) to each ml. of oxalated plasma in silicone-coated lusteroid tubes. The mixture was stirred thoroughly with a silicone-coated glass rod, incubated at room temperature for ten minutes, and then centrifuged. The supernatant barium-adsorbed plasma was then incubated at 56°C. for thirty minutes and then recentrifuged. Barium sulfate-adsorbed, heated plasma was either used upon the day of preparation or, after storage at −25°C., within a few days.

Chloroform-treated plasma was prepared by shaking 1 ml. of normal barium sulfate-adsorbed, heated plasma with 1 ml. of chloroform for one minute in silicone-coated tubes. The chloroform and precipitated material were separated by centrifugation and traces of chloroform remaining in the treated plasma were removed by aeration.

Glass-treated plasma was usually prepared by shaking 1.5 ml. of plasma with 300 mg. of crushed pyrex glass (50–100 mesh) in pyrex tubes (internal diameter, 11 mm.) for ten minutes, usually at room temperature. A mechanical shaker was usually used, but qualitatively similar results were obtained when the tubes were agitated by hand. In certain experiments treatment with crushed glass was performed in tubes coated with five coats of 5 per cent siliclad, Clay-Adams. Glass-treated plasma was stored in the same tubes in ice water and used within a few minutes of preparation. Too little plasma was available from patients deficient in Stuart factor or plasma thromboplastin antecedent to use this method. Instead, studies were performed upon plasma which had been in contact with glass during storage.

Crude Hageman factor was prepared from barium sulfate-adsorbed, heated plasma by precipitating the fraction soluble at 30 per cent saturation and insoluble at 40 per cent saturation with neutralized ammonium sulfate solution. The fraction was dissolved in barbital-saline buffer, reprecipitated at 40 per cent saturation with ammonium sulfate, and dialyzed for twenty-four hours against sodium acetate buffer at pH 5.2 and ionic strength 0.02. The precipitate was then dissolved in barbital-saline buffer and dialyzed against the same buffer for twenty-four hours. This preparation was performed at 4°C. The crude Hageman factor was stored at −25°C. until used.

A more concentrated Hageman factor was prepared from pooled, normal serum which had been stored at 4°C. for a week to insure complete clotting, adsorbed with barium sulfate and heated at 56°C. in the manner described. The fraction soluble at 30 per cent saturation with neutralized ammonium sulfate solution, but insoluble at 40 per cent saturation, was separated by centrifugation, resuspended in 40 per cent ammonium sulfate, and recentrifuged. This fraction was then dissolved in one-tenth volume of water and dialyzed against repeated changes of sodium acetate buffer at pH 5.2, ionic strength 0.15. The dialyzed fraction was then brought back to the original volume by the addition of sodium acetate buffer and adsorbed in 40 ml. aliquots, with 10 mg. of kaolin (N.F., acid-washed, American Standard, Fisher) per ml. for fifteen minutes at 37°C. The kaolin was separated by centrifugation, washed with acetate buffer and eluted with 40 ml. of an equal mixture of barbital-saline buffer and 1.0N sodium chloride solution for one hour at room temperature. The eluate was discarded after centrifugation, and the kaolin was re-eluted with one-tenth its original volume of a mixture of one part of neutralized saturated ammonium sulfate solution and three parts of 0.5M tris-(hydroxymethyl)aminomethane buffer (Sigma 7–9, Sigma Chemical Co.) at pH 7.5. The eluate was dialyzed against sodium phosphate buffer (pH 7.5, ionic strength 0.02) at 4°C., and then acidified to pH 5.2 with 1 per cent acetic acid. The precipitate, separated by centrifugation, was suspended in $\frac{1}{100}$th its original volume in barbital-saline buffer and frozen at −25°C. The yield of Hageman factor was approximately 25 per cent of that of the original serum, and its activity varied in different preparations from 100 to 500 times that of the original serum relative to the protein concentration. Hageman factor, thus prepared, was impure, containing at least five components electrophoretically. It was poorly soluble in the concentrated state, but formed a clear solution upon dilution to its original plasma volume. The preparaton of Hageman factor used was made in 1955, and stored at −25°C. without apparent loss of activity. However, once it was thawed and diluted to its original

volume, its activity appeared to decrease somewhat during incubation for twenty minutes at 25°C.

Barium carbonate-treated plasma was prepared by shaking 1.0 ml. of plasma with powdered barium carbonate (Merck) in siliclad coated tubes at room temperature for ten minutes, after which the barium carbonate was separated by centrifugation. The amount of barium carbonate used varied from 1 to 64 mg. per ml. of plasma. Plasma was treated with kaolin, aluminum hydroxide (amphojel® without flavor, Wyeth), tricalcium phosphate, super-cel (celite, Johns Mansville), animal charcoal (Fisher Scientific Co.) or magnesium-ammonium phosphate in the same manner, using as much as 256 mg. of the salt per ml. of plasma.

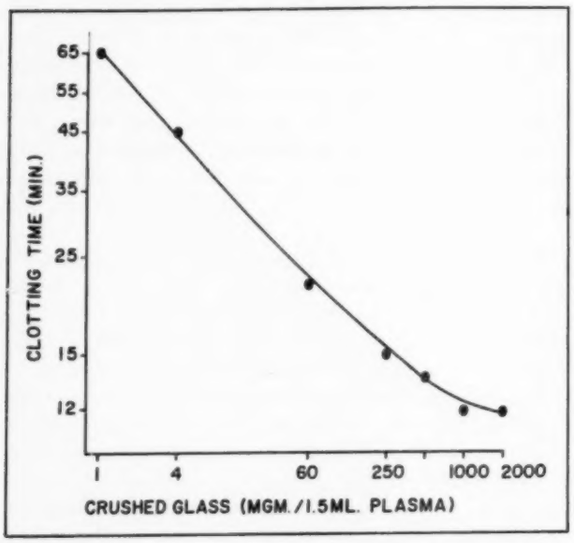

FIG. 1. The influence of crushed glass on the recalcified clotting time of normal citrated plasma. The crushed glass was agitated with 1.5 ml. of plasma. It was removed by centrifugation before the clotting time was measured.

All dialyses were performed in Visking No-Jax cellophane casings. The temperatures recorded are those of the surrounding bath, rather than of the solution incubated, to protect the solutions from the effects of the glass or metal of the thermometer. Pyrex glassware was washed with chromic acid, and silicone-coated tubes, in Dreft. The composition of the barbital-saline buffer, at ionic strength 0.15 and pH 7.5, has been described elsewhere [*8*].

Procedure. The recalcified clotting time was measured in duplicate by incubating 0.2 ml. of citrated plasma and 0.1 ml. of 0.05M calcium chloride in silicone-coated tubes (internal diameter, 8 mm.) at 25°C. The tubes were tilted once a minute; the end-point was the appearance of a firm clot. The longer clotting time of each pair is recorded in the tables. However, the contents of duplicate tubes usually clotted within two minutes of each other when the clotting time was forty minutes or less.

The effect of glass or barium carbonate upon abnormal or treated plasmas was tested by the addition of 0.1 ml. of the plasma to be tested to 0.1 ml. of normal, platelet-deficient citrated plasma. The recalcified clotting time of the mixture was then tested in the manner described, using suitable concentrations of calcium chloride.

RESULTS

(1) *The Effect of Glass on Normal Human Plasma.* The recalcified clotting time of normal human platelet-deficient plasma, prepared in silicone-coated tubes, was regularly shortened by exposure to glass. For example, in one experiment the recalcified clotting time of citrated plasma was greater than two hours in silicone-coated tubes, but was fourteen minutes in pyrex tubes. The effect of varying amounts of glass was tested by shaking 1.5 ml. of platelet deficient normal plasma with crushed glass in tubes coated with siliclad so that the crushed glass constituted the bulk of the glass to which the plasma was exposed. Under these conditions the recalcified clotting time of glass-treated plasma was progressively shortened by exposure to increasing amounts of glass. (Fig. 1.) Within wide limits, the logarithm of the clotting time was inversely proportional to the logarithm of the amount of glass used. However, above a concentration of 250 mg. of glass per 1.5 ml. of plasma the effect of glass was proportionately less. In most experiments it was convenient to use a ratio of 300 mg. of glass per 1.5 ml. of plasma.

The effect of glass could be demonstrated in plasma from which all the known clotting factors had been removed or inactivated except plasma thromboplastin antecedent and Hageman factor. Oxalated human plasma was adsorbed with barium sulfate and heated at 56°C. for thirty minutes. Such adsorbed, heated plasma was incoagulable and did not alter the recalcified clotting time of normal plasma in silicone-coated tubes. However, when the adsorbed, heated plasma was treated with glass, it accelerated the clotting time of normal blood. (Table I.) When plasma was heated at 65°C. for fifteen minutes, a temperature which inactivates Hageman factor [*12*], the clot-promoting effect of glass could no longer be demonstrated.

Hageman factor is present in plasma which has been treated with chloroform [*8*]. Normal, barium sulfate-adsorbed plasma was treated with chloroform and glass, and its clot-promoting

properties were tested. (Table I.) The clot-promoting properties of glass were demonstrable in such chloroform-treated plasma.

In sum, the clot-promoting properties of glass were demonstrable in plasma from which all known clotting factors had been removed except Hageman factor and, possibly, plasma thromboplastin antecedent.

TABLE I
THE EFFECT OF GLASS UPON NORMAL BARIUM SULFATE-ADSORBED HEATED PLASMA

Test Plasma	Clotting Time* (min.)
Barium sulfate-adsorbed, heated plasma (untreated)	>120
Barium sulfate-adsorbed, heated plasma (glass-treated)	23
Chloroformed, barium sulfate-adsorbed, heated plasma (untreated)	>120
Chloroformed, barium sulfate-adsorbed, heated plasma (glass-treated)	23

* Clotting time in silicone-coated tubes of 0.1 ml. normal citrated plasma, 0.1 ml. of the plasma to be tested and 0.1 ml. 0.05M calcium chloride. The barium sulfate-adsorbed plasma was prepared from normal oxalated human plasma and heated at 56°C. for thirty minutes in silicone-coated tubes.

(2) *The Effect of Glass on Abnormal or Animal Plasmas.* The clot-promoting effects of glass were tested upon plasmas deficient in one or another clotting factor. The technic used was adapted from the reports of Shafrir and de Vries [*4*] and Margolis [*5,6*]. The effect of glass upon hemophilic plasma may be used as an example. Platelet-deficient plasma was prepared in silicone vessels from blood obtained from a normal individual and from a patient with "classic" hemophilia. The hemophilic plasma was shaken with crushed glass and the glass was then removed by centrifugation. The normal plasma was kept in silicone-coated vessels throughout the experiment. After recalcification, the normal plasma did not clot in silicone-coated tubes during a period of two hours. (Table II.) Furthermore, hemophilic plasma, whether or not treated with glass, did not clot during this time. However, when glass-treated hemophilic plasma was mixed with normal plasma, the mixture clotted rapidly. Presumably, then, the clot-promoting effect of glass in this experiment could be elicited in plasma deficient in antihemophilic factor.

In the same way, the clot-promoting effect of glass was demonstrated in the plasma of patients thought to be congenitally deficient in Christmas factor (plasma thromboplastin component), plasma thromboplastin antecedent (PTA), proaccelerin, the precursor of serum prothrombin conversion accelerator (pro-SPCA) and Stuart factor. Moreover, plasma obtained from patients in whom the one-stage prothrombin time was prolonged as the result of liver disease or therapy with bishydroxycoumarin behaved like normal plasma when treated with glass.

TABLE II
THE EFFECT OF GLASS UPON HEMOPHILIC PLASMA

Plasma	Clotting Time* (min.)
Normal (untreated)	>120
Hemophilic (untreated)	>120
Hemophilic (glass-treated)	>120
Equal parts of normal (untreated) and hemophilic (glass-treated)	16

* Clotting time in silicone-coated tubes of 0.2 ml. of citrated plasma and 0.1 ml. 0.05M calcium chloride.

Each of the various pathologic plasmas tested contained, in common, Hageman factor. The effect of glass was tested on each of several plasmas deficient in Hageman factor, obtained from patients with Hageman trait. Unlike all other plasmas tested, glass-treated plasma deficient in Hageman factor lacked clot-promoting properties. (Table III, 1–5.) Similar results were obtained in studies of the plasma of Peking ducks. The plasma of this species is devoid of detectable Hageman factor [*12*]. When duck plasma was treated with crushed glass, it did not accelerate the clotting of normal human plasma in silicone-coated tubes. These experiments suggest that the clot-promoting effect of glass requires the presence of Hageman factor.

(3) *The Effect of Hageman-Deficient Plasma upon the Clot-Promoting Property of Glass.* Plasma deficient in Hageman factor not only lacked clot-promoting properties but in addition impeded the effect of glass upon normal plasma. Citrated plasma was prepared from a normal subject and from a patient deficient in Hageman

factor. Each plasma was added to a sample of normal plasma which had not been in contact with glass. The recalcified clotting time was then measured in silicone-coated tubes. (Table III, 5–6.) Normal plasma, treated with glass, accelerated the clotting of normal, untreated plasma. Plasma deficient in Hageman factor did not accelerate clotting. Normal plasma and plasma deficient in Hageman factor were mixed, and the mixture was treated with glass. (Table III, 7.) The clot-promoting effect of this mixture was significantly weaker than that of normal, glass-treated plasma. Thus, plasma lacking Hageman factor impeded the clot-promoting effect of glass upon normal plasma.

TABLE III
THE EFFECT OF GLASS UPON HUMAN PLASMA DEFICIENT IN HAGEMAN FACTOR

Plasma	Clotting Time* (min.)
(1) Normal, untreated	>120
(2) Normal, glass-treated	12
(3) Hageman-deficient, untreated	>120
(4) Hageman-deficient, glass-treated	>120
(5) Equal parts of normal (untreated) and Hageman-deficient (glass-treated)	>120
(6) Equal parts of normal (untreated) and normal (glass-treated)	12
(7) [Mixture of equal parts of normal (untreated) and Hageman-deficient (untreated)], glass-treated	29
(8) Equal parts of normal (glass-treated) and Hageman-deficient, (glass-treated)	14
(9) [Mixture of equal parts of normal (untreated) and Hageman-deficient (glass-treated)] glass-treated	20

* Clotting time in silicone-coated tubes 0.2 ml. of citrated plasma and 0.1 ml. 0.05M calcium chloride.

The effect of the Hageman-deficient plasma seemed to be upon the action of glass. Once glass had come into contact with normal plasma, the addition of plasma deficient in Hageman factor did not appreciably impede clotting. Thus, normal plasma and Hageman-deficient plasma were treated separately with glass. (Table III, 8.) The two glass-treated plasmas were then mixed. This mixture promoted clotting almost as well as normal glass-treated plasma alone. The same result was obtained when untreated Hageman-deficient plasma was added to normal glass-treated plasma.

Two explanations may be offered for the action of Hageman-deficient plasma. Perhaps it inhibited the evolution of the clot-promoting factor. On the other hand the clot-promoting factor may have evolved normally but may have been destroyed by the Hageman-deficient plasma. The evidence to follow suggests that the former possibility is correct, namely, that Hageman-deficient plasma inhibits the evolution of clot-promoting activity.

Margolis [*5,6*] showed that the clot-promoting activity generated in plasma by contact with glass is labile. In the experiments described in the preceding paragraphs, approximately fifteen minutes elapsed between the time that the normal and Hageman-deficient plasmas were mixed and the time that the effect of the mixture on the clotting time was measured. When normal plasma, previously treated with glass, was incubated at 25°C. with Hageman-deficient plasma for fifteen minutes in silicone-coated tubes, no appreciable loss of clot-promoting activity occurred. Thus, during a fifteen-minute period Hageman-deficient plasma did not destroy the clot-promoting activity. Presumably, then, Hageman-deficient plasma impeded the action of glass on normal plasma by some other mechanism.

As will be demonstrated subsequently in section (6), decay of the clot-promoting property induced by glass is sharply reduced at cold temperatures. Nonetheless, when plasma was treated with glass at 4°C., and the glass removed by centrifugation at this temperature, Hageman-deficient plasma still impeded the clot-promoting effect of glass upon normal plasma. These experiments suggest that the inhibitory effect of Hageman-deficient plasma was not due to the decay or destruction of clot-promoting activity.

Citrated duck plasma inhibited the clot-promoting effect of glass upon normal plasma in the same manner as human Hageman-deficient plasma.

Proof was not obtained that the inhibitory activity of Hageman-deficient plasma was necessarily related to the substance in normal plasma which reacted with glass to release the clot-promoting activity. Experiments were performed to test whether or not glass would reduce the inhibitory activity of Hageman-deficient plasma. Plasma deficient in Hageman factor was treated with glass and the glass-treated plasma was then mixed with normal, untreated plasma. This mixture was then shaken with glass and its

clot-promoting effect was tested. The inhibitory effect of the Hageman-deficient plasma was reduced but not abolished by a single treatment with glass prior to its mixture with normal plasma (Table III, 9).

TABLE IV
THE EFFECT OF HAGEMAN FACTOR ON NORMAL AND HAGEMAN-DEFICIENT PLASMA

Test Plasma	Initial Concentration of Hageman Factor Clotting Time (min.)*					
	Undiluted	1/4	1/16	1/64	1/256	1/∞ †
Normal	5	9	13	20	27	30
Hageman-deficient	5	8	13	21	35	>60

* Clotting time (25°c.) in silicone-coated tubes of 0.1 ml. citrated plasma, 0.1 ml. of crude Hageman factor, serially diluted in buffer, and 0.1 ml. 0.025M calcium chloride. Only the buffer and Hageman factor had been in contact with glass prior to the measurement of the clotting time.

† Barbital-saline buffer.

(4) *The Effect of Hageman Factor upon Hageman-Deficient Plasma.* In the preceding experiments, plasma deficient in Hageman factor was without obvious effect upon normal plasma which had previously been treated with glass. If this were the case, Hageman factor should accelerate the clotting of Hageman-deficient plasma to the same degree that it accelerates the clotting of normal plasma. Crude Hageman factor, serially diluted with buffer, was added to an equal volume of citrated plasma obtained from a normal subject or from a patient deficient in Hageman factor. The recalcified clotting time of the mixture was then tested in silicone-coated tubes. (Table IV.) Under these conditions Hageman factor accelerated the clotting time of Hageman-deficient plasma as readily as it accelerated that of normal plasma. The same results were obtained with concentrated Hageman factor. These experiments corroborate the view that the inhibitory effect of Hageman-deficient plasma occurred at some point during coagulation prior to the formation of active Hageman factor.

(5) *The Effect of Inorganic Adsorbents upon Normal and Hageman-Deficient Plasmas.* Fiala [*9*] showed that the clot-promoting effect of glass could be duplicated by exposing horse plasma to barium carbonate. In the present study clotting was accelerated when normal human plasma was agitated with barium carbonate in silicone-coated tubes. As little as 1 mg. of barium carbonate per ml. of citrated plasma was effective; maximal acceleration occurred at a concentration of 64 mg. of barium carbonate per ml. Charcoal, kaolin and super-cel also promoted clotting, while aluminum hydroxide, barium sulfate and magnesium-ammonium phosphate lacked this property in the concentrations tested, and tribasic calcium phosphate was only minimally effective at a concentration of 256 mg. per ml. of plasma.

TABLE V
THE EFFECT OF BARIUM CARBONATE UPON HUMAN PLASMA DEFICIENT IN HAGEMAN FACTOR

Test Plasma	Clotting Time* (min.)
Normal, untreated	>120
Normal, $BaCO_3$-treated	13
Hageman-deficient, $BaCO_3$-treated	>120
[Mixture of equal parts of normal (untreated) and Hageman-deficient (untreated)], $BaCO_3$-treated	23
Equal parts of normal ($BaCO_3$-treated) and Hageman-deficient ($BaCO_3$-treated)	17

* Clotting time in silicone-coated tubes of 0.1 ml. normal citrated plasma, 0.1 ml. of the plasma to be tested and 0.1 ml. of 0.05M calcium chloride. The $BaCO_3$-treated plasma was prepared by shaking 1 ml. of plasma with 10 mg. of barium carbonate for ten minutes in siliclad tubes.

Barium carbonate, like glass, did not promote clotting when mixed with plasma deficient in Hageman factor. (Table V.) Moreover, plasma from patients deficient in Hageman factor appeared to oppose the clot-promoting effect of barium carbonate upon normal plasma. Once barium carbonate had come in contact with normal plasma, the addition of Hageman-deficient plasma did not inhibit the acceleration of clotting.

(6) *The Decay of Hageman Factor in Glass-Treated Plasma.* Margolis [*5,6*] demonstrated that the active substances which appears in plasma as a result of exposure to glass is unstable and disappears when plasma is removed from contact with glass. He attributed the decay to an antagonist in plasma.

The decay of the clot-promoting property

induced in normal plasma by exposure to glass was readily demonstrable. Normal plasma, glass-treated in the usual manner, was freed of glass particles by centrifugation and then incubated at 37°C. in silicone-coated tubes. At intervals, 0.1 ml. of this glass-treated plasma was mixed with equal volumes of normal, untreated plasma and 0.05M calcium chloride. Under these conditions the clotting time of successive samples of glass-treated plasma gradually lengthened. These experiments corroborate Margolis' view that the clot-promoting activity induced by glass is labile.

TABLE VI
THE EFFECT OF NORMAL PLASMA UPON THE CLOT ACCELERATING PROPERTIES OF CRUDE "HAGEMAN FACTOR"

Test Mixture	Clotting Time* (min.)
Mixture of Hageman factor and normal plasma tested immediately	7
Hageman factor and normal plasma incubated separately for two hours, mixed and then tested	7
Hageman factor and normal plasma mixed, incubated for two hours and then tested	26

* Clotting time (25°C.) in silicone-coated tubes of 0.1 ml. crude Hageman factor, 0.1 ml. normal citrated plasma and 0.1 ml. 0.025M calcium chloride. The Hageman factor was first glass-treated, but the same results were obtained without this pretreatment. Hageman factor and normal plasma were incubated at 37°C. for two hours in silicone-coated tubes.

As Margolis reported, the decay was not the result of "spontaneous" denaturation of the clot-promoting property. Even a crude glass-treated concentrate of Hageman factor was quite stable at 37°C. for at least two hours. The same preparation, mixed with normal plasma, rapidly lost its clot-promoting activity. (Table VI.) The property of normal plasma which resulted in the deterioration of clot-promoting activity resisted heating at 65°C. for fifteen minutes. The rate at which the clot-promoting activity deteriorated was directly dependent upon the temperature at which the plasma was incubated; virtually no deterioration of the clot-promoting property occurred at 2°C. Only preliminary studies have been made of the kinetics of destruction of the clot-promoting property of glass-treated plasma. These studies suggest that the clot-promoting property is destroyed enzymatically; deterioration appears to follow the equation for a zero-order reaction.

The property of plasma which produced decay of the clot-promoting activity was present in that fraction which was soluble at half-saturation with ammonium sulfate. This fraction could be freed of contaminating traces of Hageman factor either by incubation at 37°C. or by dialysis against dilute acetate buffer at pH 5.2 and ionic strength 0.02; the decaying property remained in solution. When crude Hageman factor was incubated with this fraction, its clot-promoting activity for normal plasma deteriorated and, *pari passu*, its capacity to correct the defect in Hageman-deficient plasma was lost. These observations corroborate the view that the clot-promoting property of glass-treated plasma can be identified with Hageman factor.

The property which produced decay of the clot-promoting activity was present in plasma obtained from patients with Hageman trait. The destructive activity of such plasma did not appear to be greater than that obtained from normal subjects.

COMMENTS

The factors maintaining the fluidity of blood within blood vessels are unknown. When blood is shed and placed in tubes lined with paraffin or silicone, it clots slowly, but when the same blood is put into glass tubes, coagulation is rapid. The experiments herein described confirm the view that the clot-promoting effect of glass requires the presence of a specific clotting factor [*4–6*]. Evidence has been presented that this specific substance is absent from the plasma of patients with Hageman trait and from ducks, a species in which the plasma behaves as if deficient in Hageman factor.

Hageman trait is a curious familial disorder in which the clotting time of venous blood is greatly prolonged [*8,12*]. Nonetheless, patients with this syndrome do not exhibit even trivial evidences of a bleeding tendency. The plasma of patients with Hageman trait lacks a clotting factor which can be separated from all other described clotting factors. This substance, Hageman factor, is essential for the initial stages of clotting in glass tubes. Why patients lacking Hageman factor do not have any bleeding tendency has not yet been explained. Presumably, the initiation of clotting when blood vessels are severed surgically or

accidentally is not comparable to the initiation of clotting in glass tubes.

The mechanism by which glass exerts its clot-promoting effect was studied in experiments in which normal plasma and plasma deficient in Hageman factor were mixed prior to treatment with glass. These demonstrated that human or duck plasma deficient in Hageman factor impeded the clot-promoting effect of glass upon normal plasma. However, Hageman-deficient plasma did not appreciably oppose the clot-promoting properties of normal plasma which had already been treated with glass. The same results were obtained when barium carbonate was used to promote clotting in place of glass. These experiments suggest that Hageman-deficient plasma may contain an inhibitor which interferes with the action of glass or barium carbonate upon normal plasma.

The demonstration of a similar inhibitor in normal human plasma has been elusive because of the simultaneous presence of Hageman factor. There is, however, indirect evidence for its presence. A euglobulin fraction can be precipitated from normal human plasma by acidification and dilution. This euglobulin accelerates the clotting of normal plasma even though neither fraction nor plasma has been allowed to come in contact with glass [*13*]. Evidence has been presented earlier that the clot-promoting effect of this euglobulin fraction is related to its content of Hageman factor [*8*]. Perhaps the precipitation separates Hageman factor from an inhibitory agent. However, proof that such an inhibitor is present in untreated normal plasma has not yet been achieved. The fact that treatment with glass reduced the clot-delaying activity of Hageman-deficient plasma suggests that suitable technics will demonstrate the inhibitor in normal plasma.

Previous investigators have suggested that glass promotes clotting through its action upon clotting factors other than Hageman factor. None of the experiments described in this report negates the possibility that glass, or barium carbonate, accelerates clotting by mechanisms additional to their effect on Hageman factor. Indeed, unpublished studies [*12*] have demonstrated that the clotting time of whole blood obtained from patients deficient in Hageman factor is accelerated by agitation with glass. Whether or not this effect is mediated via platelets is not known.

Margolis [*5,6*] has also demonstrated that the clot-promoting activity induced in plasma by treatment with glass is labile; this destruction of activity appeared to be due to the presence of an antagonist in plasma. This observation has been confirmed. Evidence has been presented suggesting that plasma normally has enzymatic activity which causes decay of the clot-promoting activity. The same enzymatic activity was demonstrable in the plasma of patients with Hageman trait. However, this destructive activity did not appear to be related to the inhibition of the action of glass by Hageman-deficient plasma.

The experiments described suggest the following tentative hypothesis. In normal plasma, Hageman factor is present in an inactive state. The inactive state probably results from the presence of one or more inhibitors directed against Hageman factor. The fluidity of blood within blood vessels is maintained by these inhibitors. Exposure of blood to glass or to such other adsorbents as charcoal, kaolin or barium carbonate converts Hageman factor to an active form, initiating clotting. Presumably, these adsorbents free Hageman factor from inhibition. Once Hageman factor has become active, however, it is rapidly destroyed by an enzyme, a mechanism which may protect against its continued action. Similar events may lead to the formation of intravascular thrombi. Perhaps under some circumstances the initiating event in thrombosis is a change in the vascular endothelium in such a way that its surface takes on certain properties of glass. Such changes have been described by Moolten and his associates [*14*] in the endothelium of dying rabbits. The endothelial surface, so damaged, would then serve as a focus at which the changes leading to intravascular clotting would begin. Further experiments are needed to test the validity of this hypothesis and to elucidate the mechanism by which Hageman factor, freed from inhibition, initiates clotting.

Plasma, then, may contain two inhibitory mechanisms related to the initiation of clotting, one preventing the activation of Hageman factor and the other destroying Hageman factor which has become activated. The question arises whether or not certain hemorrhagic disorders associated with prolongation of the clotting time but not yet clearly defined may be the result of alterations of these inhibitory properties. Further studies will be required to demonstrate the validity of this possibility.

SUMMARY

Evidence is presented that the clot-promoting effect of glass or of certain other adsorbents upon normal human plasma requires the presence of Hageman factor. Human or duck plasma, deficient in Hageman factor, inhibited the clot-promoting effect of glass or barium carbonate upon normal human plasma. The clot-promoting property of normal plasma, once activated, deteriorated rapidly, apparently as the result of enzymatic destruction. These observations suggest that the fluidity of blood within blood vessels may be maintained by inhibitors directed against Hageman factor.

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Quantitative Measurement of Gastrointestinal Blood Loss*

I. The Use of Radioactive Cr^{51} in Patients with Gastrointestinal Hemorrhage

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CLASSICALLY, cases of iron deficiency anemia due to chronic gastrointestinal blood loss are detected by a history of tarry or bloody stools and/or the presence of occult blood in the feces, hypochromia of the red cells, and x-ray or endoscopic evidence of a lesion. This communication is concerned with those cases of chronic gastrointestinal blood loss which lack many of these findings and masquerade as cases of anemia of obscure etiology. The use of radioactive $Na_2Cr^{51}O_4$ for measuring twenty-four-hour fecal blood loss in conjunction with the frequent collection of fluid from various levels of the gastrointestinal tract from a Cantor or Miller-Abbott tube for radioactive counting and chemical testing for blood will be described.

METHODS

Collection and Preparation of Fecal Samples. Four-day fecal collections were made by placing a tared stainless steel gallon blender† under a portable commode. The blender was weighed after the feces were collected, and 2 to 5 parts by weight of water were added to 1 part of feces. The feces were then thoroughly homogenized and 4 to 5 gm. aliquots placed in tared 6 ml. screw top vials, the exact amount being determined by weighing the vials after addition of the feces.

Radioactive Labeling of Red Cells with Radioactive Sodium Chromate. Ten to 20 cc. of whole blood was removed from the patient and placed in a sterile 75 ml. container‡ with 4 to 9 ml. of ACD.§ One to 3 microcuries of $Na_2Cr^{51}O_4$ per kg. of patient body weight were added to the whole blood. The final concentration of metallic chromium per ml. of whole blood was between 1 and 10 μg. per ml. The chromium blood mixture was then allowed to stand at room temperature for one hour with gentle mixing every ten to twenty minutes, and a measured amount, usually from 10 to 20 cc. of this labeled blood was injected into the donor patient. The injected chromium labeled blood was not washed after it had been tagged *in vitro*. With the above technic previous work has shown that from 80 per cent to 95 per cent of the chromium^{51} becomes bound to the red cells [*1*]. Of the 10 per cent to 15 per cent of the chromium^{51} which remains in the plasma of the injected blood only 10 per cent of this (or 1 to 1.5 per cent of the injected Cr^{51}) has been demonstrated ultimately to tag the patient's red cells after injection [*1*].

Radioactive Counting. The Cr^{51} in the specimens were then assayed in a well-type scintillation counter. A Cr^{51} standard was counted every one or two hours during the day and used to correct for the physical decay of chromium^{51} or any possible variation in the behavior of the detection equipment. All samples were expressed as a ratio of this standard. Sufficient samples and background counts were made to give a statistical counting error of ±5 per cent (1 standard deviation) or less [*2*]. The number of milliliters of

† Central Scientific Company.

‡ Fenwal "minivac," Ashland, Massachusetts.

§ Acid citrate dextrose (75 ml. contains trisodium citrate, 1.65 gm., citric acid, 0.60 gm., and dextrose, 1.84 gm.).

* From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., and the Dartmouth Medical School and Hitchcock Hospital, Hanover, New Hampshire. Supported in part by Grant A-1149, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland. Portions of this paper were presented before the Combined Clinical Staff Meeting of the National Institutes of Health on October 13, 1955, Bethesda, Maryland.

whole blood contained in the stool sample was determined by the following formula:

$$\frac{\text{Total Cpm in the stool}}{\text{Average Cpm/ml. of circulating blood on first and last day of stool collection}}$$

where Cpm = counts per minute, and the total Cpm of the stool collection = Cpm per gm. of homogenized stool × the total weight of the homogenized stool sample. The number of milliliters of whole blood contained in the stool as found by the above formula are then divided by the number of days of the stool collection.

TABLE I
RADIOACTIVE Cr^{51} CONTENT OF STOOL EXPRESSED AS EQUIVALENT ML. OF WHOLE BLOOD

Diagnosis	Age (yr.), Sex	Days Feces Were Collected after Injection of Cr^{51} Red Blood Cells	Apparent Blood/ Day (ml.)
Polycythemia	34, M	2–5	0.8
Sickle cell trait	40, M	2–6	1.9
Parkinsonism	76, M	11–15	0.4
Scleroderma	35, F	0–2	1.5
		4–5	1.4
		5–6	0.9
Sickle cell anemia	19, M	13–17	1.5
Normal	20, M	3–8	2.8
		10–14	1.2
		22–25	1.8
Rheumatoid arthritis	40, F	0–4	0.3
		4–8	0.6
Rheumatoid arthritis	48, M	1–5	1.3
Mean ± S.D.			1.2 ± 0.5*

* Mean ± standard deviation. In subjects in whom more than one stool collection was made, the average value was used in computing the mean.

Occult Fecal Blood Tests. The occult fecal blood tests were carried out by the benzidine dihydrochloride method as follows: Three drops of benzidine dihydrochloride solution* were added to a thin smear of feces on white bibulous or filter paper. Next, three drops of 2.9 per cent aqueous solution of hydrogen peroxide* were added to the fecal smear. The time for the development of a green or blue color was recorded in seconds. Experience to be described later in the paper indicated that any color development in fifteen seconds was indicative of abnormal amounts of blood being present. A color reaction which developed between fifteen and sixty seconds might or might not indicate increased abnormal gastrointestinal blood loss.

Serum iron was measured by the method of Peterson [3].

* 1 gm. of benzidine dihydrochloride to which were added in the following order: 20 ml. of glacial acetic acid, 30 ml. of water, and 50 ml. of 95 per cent ethyl alcohol. The benzidine reagent was stored in a dark glass bottle at 5°c.

RESULTS

Apparent Blood Content of Normal Stools as Determined by Radioactive Sodium Chromate. The equivalent radioactivity of 1.2 ± 0.5 (range 0.3 to 2.8) ml. of whole blood per day was present in thirteen of the two to four-day stool collections of eight different patients (Table I) aged nineteen to seventy-six years who had previously received Cr^{51} labeled erythrocytes. The stool collections were taken at various intervals as indicated in Table I after the injection of the tagged blood. All of these patients had been observed for a period of at least three months prior to time of the study, and with the exception of Case V (sickle cell anemia) all had a normal Cr^{51} autotransfused red cell survival [1]. All the patients in Table I had at least three negative routine benzidine occult blood tests before they were studied. The term "apparent" ml. of whole blood is used in Table I because we have no evidence that this figure represents in its entirety blood shed into the gastrointestinal tract and not a sum of the excretion of Cr^{51} into the bowel as it is released from the tagged blood and the actual shedding of blood into the gut.

The Sensitivity of the Benzidine Dihydrochloride Test. The benzidine dihydrochloride test used in this study gave a positive result in thirteen seconds when one drop of 5 mg. per cent hemoglobin solution was present in aqueous mixture on the filter paper and a positive reaction in one-half a minute to one drop of 2.5 mg. per cent of an aqueous hemoglobin solution. (Table II.)

Of more importance, however, is the sensitivity of the benzidine test to hemoglobin when present in the stool. In Table III it can be seen that sensitivity is much reduced when known amounts of hemoglobin are mixed with homogenized feces (6 part feces plus 4 to 5 parts water). It takes a 400 mg. per cent solution of hemoglobin in homogenized stools to give a

* 1 ml. of 29 per cent superoxol® (Merck) plus 9 ml. of H_2O.

positive test in fifteen seconds and 300 mg. per cent to give a positive test in one minute. (Table III.) The reason for this eighty to 120-fold decrease in sensitivity was not fully determined in this study. No convincing evidence of inhibitory substances in the stool was obtained. This lack of sensitivity may be due to the interference of the brownish color of the stool with the visual detection of the color reaction, since mixtures of hemoglobin solution with various inert dyes which approximate the color of a stool showed the same order of magnitude of decreased sensitivity.

TABLE II
SENSITIVITY OF BENZIDINE DIHYDROCHLORIDE TO AQUEOUS SOLUTIONS OF HEMOGLOBIN

Hemoglobin (mg. %)	Seconds for Positive Test to Develop
37.5	4
30.0	4
15.0	6
10.0	7
5.0	13
2.5	24

Recovery of the Radioactivity from Feces After Oral Ingestion of Cr^{51} Labeled Red Cells. In order for the estimation of the amount of blood in the stool by Cr^{51} to have validity, it must be demonstrated that the radioactivity of tagged blood once present in the gastrointestinal tract is entirely excreted and not reabsorbed. An average of 98.9 ± 9.7 per cent of Cr^{51} administered orally as Cr^{51} labeled red cells was recovered in the six-day fecal collections of ten subjects. (Table IV.) Less than 0.5 per cent of the Cr^{51} was recovered in a five-day urine collection and less than 0.2 per cent of the ingested Cr^{51} was present in the circulating blood of the twenty-one year old man who drank 20 ml. of blood. (Table IV.)

When approximately 400 μg. (chromium content) of sodium chromate was administered in the form of $Na_2Cr^{51}O_4$ salt dissolved in grape juice, 96.3 per cent and 92.8 per cent of the Cr^{51} was recovered in five-day fecal collections from two subjects. When Cr^{51} was fed in the form of 100 ml. plasma tagged with 90 μg. (chromium content) of chromic^{51} chloride 97.6 per cent was present in five-day fecal collections.

TABLE III
MINIMUM CONCENTRATIONS OF HEMOGLOBIN DISSOLVED IN WATER AND FECES RESULTING IN A POSITIVE BENZIDINE DIHYDROCHLORIDE TEST

Hemoglobin	Time for Color Development	
	15 Seconds (mg. %)	60 Seconds (mg. %)
Hgb. in H_2O	5.0	2.5
Hgb. in stool	400	300

TABLE IV
PER CENT RECOVERY OF INGESTED CR^{51} LABELED BLOOD

Age (yr.), Sex	Blood Ingested (ml.)	Dose in Feces 0–5 Days (%)
20, M	580	98
23, M	80	96
22, M	80	98
22, M	80	109
23, M	80	102
22, M	70	116
76, M	50	93
45, M	20	91
21, M	20	99
50, M	20	87
Mean ± S.D.		98.9 ± 9.7

Since it has been demonstrated that radioactive Cr^{51} when administered as a salt is not reabsorbed, it cannot be concluded from these data how much if any of the hemoglobin is reabsorbed. But it can be concluded that for practical purposes once chromium tagged blood is shed into the gastrointestinal tract all the radioactivity will be recovered in the stool and, therefore, radioactive Cr^{51} represents an accurate maximum estimate of the amount of shed blood in a patient who has Cr^{51} tagged red cells.

Nine patients suspected of blood loss were studied. (Table V.)

CASE STUDIES

CASE I. A sixty year old white man was referred to the Institute on April 15, 1955, because of "hemolytic anemia" associated with chronic rheumatoid arthritis. The patient had been known to have an anemia for the past two years. He had been taking 100 mg. of cortisone a day for six months before admission. On two occasions before admission an attempt was made to decrease the steroid dosage. Each time this was

done the referring physician noted that the hematocrit fell to 20 per cent from the usual level of 30 to 35 per cent. Resumption of cortisone was accompanied by a transient reticulocytosis and a return of the red cell volume to 30 ml. per cent. On admission to the National Institutes of Health (N. I. H.) no spleen, liver,

TABLE V
CASES OF GASTROINTESTINAL BLOOD LOSS STUDIED

Case No.	Age (yr.), Sex	Diagnosis	Blood in Stool/Day (ml.)
I	60, M	Hiatus hernia	345
II	40, F	Ulcer of ileum	.....
III	35, F	Ulcer of ileum	68
IV	45, F	Carcinoma of cecum	.....
V	35, M	Duodenal ulcer	18
VI	74, F	Marrow failure	17
VII	20, M	Normal	1.5
VIII	65, M	Leiomyoma of the ileum	7.5
IX	14, M	Hemangioma of jejunum	60

or lymph nodes were palpable. Admission laboratory work-up revealed a hematocrit of 30 per cent with a mean corpuscular hemoglobin (MCH) of 19 $\mu\mu$g. per cent, a mean corpuscular volume (MCV) of 62 cubic microns, a mean corpuscular hemoglobin concentration (MCHC) of 31 gm. per cent, and a reticulocyte count of 1 per cent. Three stools were negative for occult blood. Serum iron was 32 μg. per cent, the Coombs' test was negative, and the serum bilirubin 0.1 mg. per cent. An upper gastrointestinal series revealed a hiatus hernia. A small bowel series revealed no abnormalities, and the barium enema revealed multiple diverticula of the descending colon. The patient denied any symptoms attributable to the hiatus hernia or passage of bloody or tarry feces. During the first three weeks after admission the patient maintained a hematocrit of 30 to 33 ml. per cent. Cortisone was decreased at the rate of 25 mg. every two days and 3.6 gm. of aspirin per day was begun. The patient was given 1 gm. of iron intramuscularly in the form of iron dextran* (imferon®) as a part of another study. On May 20, 1955, the hematocrit fell to a minimum value of 20 per cent (Fig. 1); on June 7, 1955, a reticulocytosis of 10 per cent was noted. The fall in hematocrit occurred without any noticeable change in symptoms. No feces were tested for occult blood during this period. Without any therapy other than aspirin the hematocrit gradually increased as shown in Figure 1.

On June 23, 1955, a chromium^{51} autotransfused red cell survival study was started. (Fig. 1.) Five different fecal samples tested for occult blood were negative in the interval of June 15 to June 26. On August 2, 1955, the hematocrit again fell and at this time the patient acknowledged some increased fatigue, and a slight tachycardia of 100 per minute was noted. Because of these symptoms he was transfused with two units of blood. (Fig. 1.) At this time the feces were persistently positive for occult blood although they were not tarry. Feces collected from August 6 to August 9 showed that he excreted radioactive chromium equivalent to 1,040 ml. of whole blood. (Fig. 1.) The red blood cell chromium^{51} survival (Fig. 1) during this interval was short and was consistent with hemolytic anemia or blood loss. The fecal studies made it clear, however, that the shortened red blood cell survival was due to blood loss. The hemoglobin again rose after this second episode of bleeding to its usual level of between 30 and 33 volumes per cent. At this time the patient was given 2 gm. of intramuscular iron.

A third episode of a falling hemoglobin occurred from September 21 to September 25; at this time he was found to have radioactivity in his stools equivalent to 630 ml. of blood. (Fig. 1.) This was also accompanied by a shortened cell survival as evidenced by the second autotransfusion studies started on September 19, 1955. (Fig. 1.) On August 4, a Cantor tube was placed in the stomach and gross blood was persistently obtained over a period of four hours. A diagnosis of an ulcerated bleeding hiatus hernia was made. The hiatus hernia was repaired on October 8, 1955. During the operation the patient received 5 units of blood, and on the second postoperative day the hematocrit was 40 per cent and remained at this level for the next two months. The patient was last seen in October 1956 when his hematocrit was 51 per cent, the MCHC 31 gm. per cent, and the serum iron 36 μg. per cent.

Comment: Initially this patient was thought to have a hemolytic anemia as part of the disease picture of active rheumatoid arthritis. The delay in making a correct diagnosis of blood loss anemia was due to the fact that our index of suspicion for bleeding lesions was not high enough and too much reliance was placed on negative fecal occult blood tests and the lack of a history of bloody or tarry feces. The finding of gross blood in the stomach tube specimen indicated that the bleeding was probably due to the hiatus hernia and not to the diverticula of the colon. The potential danger to the patient was made apparent by quantitating the blood lost in the feces, although the magnitude of blood lost in this case was suspected from the marked drop in the hematocrit.

CASE II. A forty year old white woman first entered the N. I. H. in 1954 with a chief complaint of anemia of two years' duration. Laparotomy had been per-

* Imferon®—Lakeside Laboratories, Cleveland, Ohio.

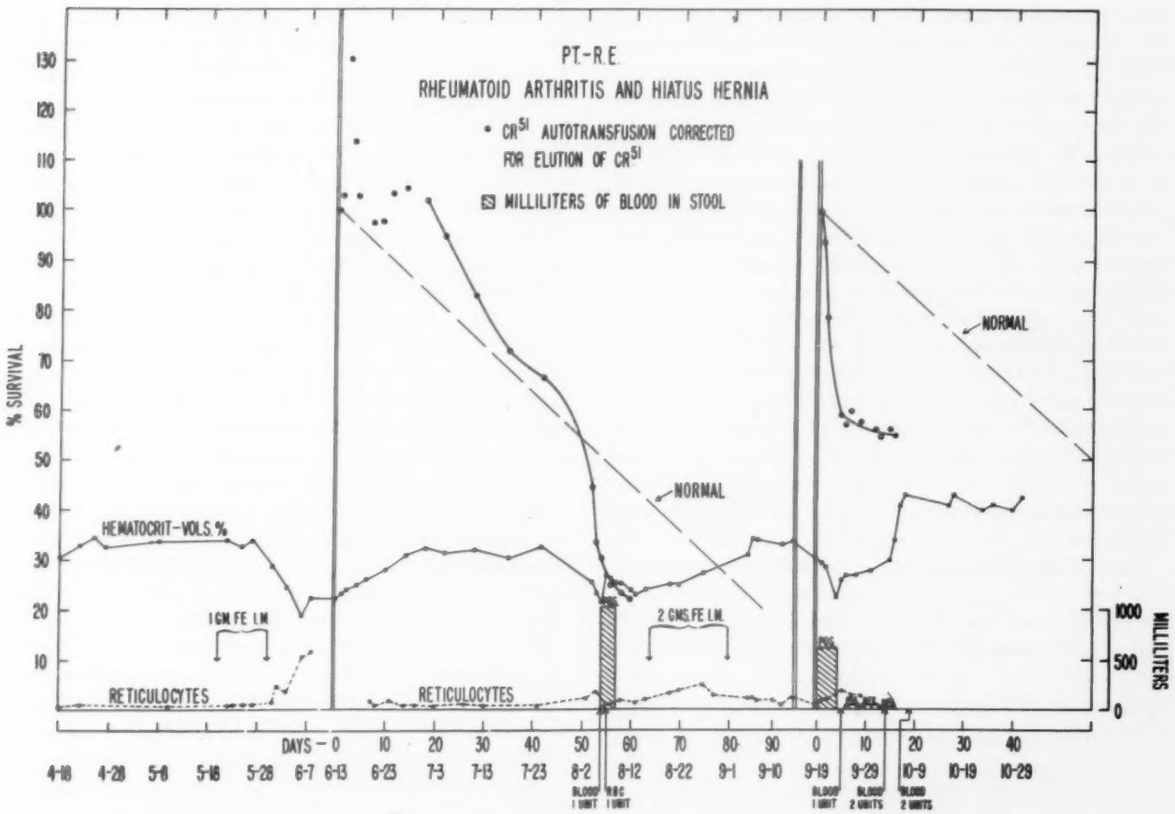

FIG. 1. Cr^{51} autotransfused red cell survival and fecal blood excretion data for Case 1. The vertical axis on the right labeled "milliliters" is the ordinate for ml. of blood found in the feces, and on the left is a percentage which is the ordinate for the Cr^{51} red blood cell survival curve, hematocrit and reticulocyte count. The curves designating the hematocrit and reticulocyte are labeled as such. The unhatched, dashed straight line is the normal Cr^{51} red blood cell survival corrected for elution [7] and the adjacent solid line the Cr^{51} red blood cell survival in the patient also corrected for elution of Cr^{51} [7].

formed in 1935 and a diagnosis of tuberculous peritonitis had been made. In 1946, 20 inches of gangrenous small bowel were resected (volvulus of the small bowel). In 1952, the patient was first told that she was anemic and was placed on intermittent vitamin B_{12} therapy, intravenous iron injections, liver injections and oral ferrous sulfate. At one time during this interval it was thought that she had responded to iron but apparently her physicians were not sufficiently convinced of this to persist in iron therapy or seek the source of possible blood loss.

On admission physical examination revealed a pale, chronically ill-appearing patient who had no lymphadenopathy, palpable organs, or masses in the abdomen. The hematocrit was 36 per cent, hemoglobin 10.9 gm. per cent, reticulocytes 0.9 and 1.7 per cent, MCHC 30.5 gm. per cent, MCV 86 μ^3, and MCH 26 $\mu\mu$g. The serum iron was 52 μg. per cent and the total iron binding capacity 180 μg. per cent. The hematocrit gradually fell to 24 per cent during the hospital stay of two months. An aspirated bone marrow was interpreted as normal. One of the two fecal specimens was positive for occult blood. The patient was given two blood transfusions and discharged with a diagnosis of aplastic anemia.

She was readmitted for further study of her anemia in March 1955. The hematocrit was 26.5 per cent, hemoglobin 8.6 gm. per cent, reticulocytes 2.2 and 2.5 per cent, MCHC 32.5 gm. per cent, MCV 77 μ^3, MCH 26 $\mu\mu$g., and the serum iron 14 μg. per cent Multiple fecal samples were positive for occult blood. An upper gastrointestinal series showed a diverticulum of the second part of the duodenum, but otherwise was within normal limits. Small bowel series and barium enema were negative. Two proctoscopic examinations revealed no abnormalities. A Cantor tube was passed and allowed to progress through the gastrointestinal tract for three days. The approximate position of the tube was estimated by x-ray. During the time the tube was passing from the pylorus to the jejunum there were seventeen negative occult blood tests on the samples removed, and four slightly positive tests. When the tube was estimated to be in the terminal ileum, seven positive and one negative test were obtained. Barium sulfate was then instilled into the tube, the tube removed and x-ray pictures taken. A

suspicious diverticulum-like lesion was seen at what was thought to be the junction of the jejunum and the ileum (the site of the previous bowel anastomosis); however, a Meckel's diverticulum could not be ruled out. Because of these findings a diagnosis of a bleeding lesion in the region of the terminal ileum was made. At operation the entire large bowel and the small bowel were manually palpated and felt to be normal. The site of the previous anastomosis was found and appeared to represent a side-to-side ileojejunal anastomosis. This anastomosis was removed and an end-to-end anastomosis established. Gross examination of the specimen revealed an ulcer in the proximal portion of the blind loop in the side-to-side anastomosis. The ulcer had a flat base and measured 2.5 cm. in greatest dimension. Microscopic study revealed extension of the ulcer into the submucosa, but careful study revealed no evidence of a granulomatous inflammation. Smears and culture of the tissue from the bed of the ulcer were negative for acid-fast bacilli.

Two weeks after surgery the patient was started on oral iron therapy which was continued for one year. A normal hemoglobin has been maintained for the one and a half years following operation.

Comment: This patient, who at one time during her course had what was interpreted as a normochromic anemia, and occult blood tests of the feces equivocal for blood loss, is presented as an example of a case of proved gastrointestinal ulceration. The failure to develop unequivocal hypochromia (MCHC 30 gm. per cent) is surprising, particularly during the second admission when the serum iron was 14 μg. per cent. After further study the correct diagnosis of gastrointestinal blood loss anemia was made because of persistently positive tests of occult blood in the feces. The use of the Cantor tube proved decisive in localizing the level of bleeding. Stains of the bone marrow for iron, frequent occult blood tests of the feces and a higher index of suspicion on the part of all her physicians might have led to an earlier diagnosis in this case.

CASE III. A thirty-five year old woman entered the N. I. H. in May 1954 with the chief complaint of anemia and diarrhea of two years' duration. The patient stated she had had "nine feet" of her small bowel removed in 1952 because of a regional ileitis. Since 1952 the patient had been treated for hypochromic anemia with intermittent oral iron therapy, at least 3 gm. of saccharated iron oxide injected intravenously, and blood transfusions. During this period the hemoglobin reportedly ranged between "30 per cent and normal." X-ray studies revealed a shortened small bowel and an ileal transverse colostomy as the only abnormalities. Because of the persistent anemia and positive occult blood tests of the feces, the patient was subjected to a second laparotomy one year before admission. However, the patient was told that no specific lesion was found at operation and therefore no tissue was removed.

Physical examination on admission revealed a pale, chronically ill-appearing woman. Hematocrit was 30 per cent, hemoglobin 8.7 gm. per cent, reticulocytes 1.1 per cent, MCHC 29 gm. per cent, MCV 63 μ^3, MCH 18 $\mu\mu$g., and the serum iron 24 μg. per cent. Two four-day fecal collections revealed 59 and 39 ml. of blood per day in the feces. The presence of a chronic blood loss anemia was obvious from the hypochromia of the red cells and the presence of occult blood in the feces. X-rays of the entire gastrointestinal tract revealed only a shortened small bowel and a transverse ileocolostomy. Repeat x-ray studies were again within normal limits. While in the hospital the patient received 1 gm. of saccharated iron injected intravenously.* This was followed by a reticulocytosis of 10 per cent and a rise in the hemoglobin concentration to 12 gm. per cent. Soon after admission, the patient also received hydrocortisone in a dosage of 80 mg. per day. By September 1954, the diarrhea had remitted. It was decided at this time that insufficient evidence existed for the presence of a discrete bleeding lesion and that a diffuse bleeding inflammatory lesion of the bowel existed. Therefore, the patient was discharged from the hospital on steroid and iron therapy.

Following discharge the anemia recurred and the patient was readmitted in June 1955 for further studies. Hematocrit was 22 per cent, hemoglobin 6.3 gm. per cent, reticulocytes 4 per cent, MCHC 28.5 gm. per cent, MCV 72 μ^3, MCH $\mu\mu$g., and the serum iron 4 μg. per cent. The four-day fecal collections revealed an average of 68 and 86 ml. of blood in the feces per day. Upper gastrointestinal small bowel series and barium enema again revealed no abnormalities. Shortly after admission a Cantor tube was passed and five samples which were negative for occult blood and Cr^{51} were obtained from the duodenum, four samples which were positive for occult blood but containing no significant radioactivity (Cr^{51}) from the mid-jejunum, five samples which were negative for occult blood and Cr^{51} from the proximal ileum, and nine samples which were positive for occult blood and Cr^{51} (5 ml. of fluid contained four times background counts) from the terminal ileum. The results were interpreted as showing a bleeding lesion in the region of the terminal ileum or in the region just proximal to the anastomosis with the large bowel. Four samples obtained in the mid-jejunum were chemically positive for occult blood, but these were not considered indicative of abnormal amounts of blood because they contained no measurable amount of radioactivity.

Two four-day stool collections revealed an average

* Feojectin.®

blood loss of 68 and 87 ml. per day. A preoperative diagnosis of a bleeding lesion at the site of the anastomosis was made.

At operation an annular band of scar tissue was seen just proximal to the site of anastomosis of the small bowel to the transverse colon. Because the cecum, ascending and transverse colon appeared normal, an ileocecostomy was performed. Gross examination of the operative specimen showed a circular, elevated area 1 cm. in diameter covering the entire circumference of the mid-portion of the specimen. Microscopic examination revealed the mucosa to be entirely absent from this area and the ulcerative lesion to extend around the entire circumference of the ileum 1 cm. in width. Lymphocytic infiltration of the submucosa was noted. The amount of connective tissue in the submucosa was increased; the musculature was intact. There was no granulation tissue. The mucosal and mural structure of the ileum adjacent to this lesion was entirely normal. There were no changes suggestive of regional ileitis. Ten days after the operation the amount of blood in the stools was again measured by the chromium^{51} technic, and 24 ml. per day were found to be present during a four-day period.

During the two-year follow-up period after the patient's operation she maintained a normal hemoglobin and required no blood transfusions, or iron therapy.

Comment: This patient illustrates the value of quantitating the amount of blood loss in the feces. The large amounts of blood lost were not apparent from the gross examination of the feces which were not tarry, but might have been suspected from the severe anemia of the patient. Also the usefulness of the Cantor tube in localizing a lesion not detected by x-ray was again demonstrated in this patient. The value of correlating the benzidine occult blood test on the intestinal secretions with radioactive counting is demonstrated in this patient, since it would appear from the postoperative course that no significant blood loss has occurred from the jejunum.

Case IV. A forty-five year old white woman was admitted to the hospital with a chief complaint of anemia of eighteen months' duration. During the interval before admission the patient had received large but unknown amounts of oral and intravenous iron, vitamin B_{12}, and blood transfusions. Fourteen months before admission a hysterectomy and right oophorectomy were performed because of metrorrhagia. Seven months before admission a diagnosis of hemolytic anemia was made because of increased reticulocytosis, spherocytes on a stained blood smear, increased osmotic fragility of the red cells, and erythroid hyperplasia of the marrow. Splenectomy was performed with no effect on the anemia. A few weeks after splenectomy the patient noted the onset of pain in the epigastric area, much worse at night than during the day. The patient described the pain as being like "labor pain" with some cramping and nausea. The pain was relieved in the upright position. Physical examination on admission in May 1954 revealed no palpable liver, spleen, or abdominal masses, and no lymphadenopathy. External and internal hemorrhoids and an anal fissure were present. Laboratory studies revealed a hypochromic anemia with hemoglobin of 5.4 gm. per cent, MCHC 27.6 gm. per cent, and multiple fecal samples were positive for occult blood. The Coombs' test was negative, and the patient had 2 per cent reticulocytes. Upper gastrointestinal series showed a small hiatus hernia. X-rays of the small and large bowel were normal. Esophagoscopy revealed peptic esophagitis with ulceration. A diagnosis of bleeding due to hiatus hernia was made. The patient was given 4 gm. of iron intravenously, a bland low calorie diet, antacids, and tincture of belladonna. One month later the hemoglobin had risen to 9.6 gm. per cent and the hematocrit to 32 ml. per cent. The reticulocytes rose to 12 per cent on the twelfth day of the iron injections. The patient was discharged with instructions to take 0.9 gm. of oral ferrous sulfate daily.

During the next six months the epigastric pain continued unabated and she noted red blood in her stools. In November, 1955, she was admitted for further studies. Sigmoidoscopy and anoscopy revealed only the external and internal hemorrhoids and the anal fissure. The hemorrhoids and the fissure were excised. During a six months' interval no blood was noted in the stools.

Because of the persistence of epigastric symptoms and the hypochromic anemia, the patient was readmitted in January 1955 and the hiatus hernia repaired. This operation resulted in a complete relief of the epigastric symptoms.

The patient was readmitted in March 1955 because of lower abdominal cramping and vomiting. She denied epigastric pain. Physical examination revealed the abdomen to be soft and non-tender, and no organs or masses were palpable. The hemoglobin was 12 gm. per cent, hematocrit 38 per cent, and MCHC 33 gm. per cent. Flat films of the abdomen revealed two distended loops of small bowel in the mid-abdomen with fluid levels. A small bowel series, however, did not show any intrinsic lesion of the small bowel but did show delayed passage of barium. Sigmoidoscopy was negative to 16 cm. A Cantor tube was passed and all samples collected were negative for occult blood until the region of the proximal ileum was reached. At this point all samples were positive for blood. A preoperative diagnosis of a bleeding lesion between the proximal ileum and the sigmoid was made. At operation a carcinoma of the cecum was found. In

addition, a carcinomatous adhesion was found between the free loop of the sigmoid and the ileum. The cecum and the transverse colon with the regional nodes were resected and ileocolostomy performed. Ten days later a second operation was performed and an 18 cm. segment of the sigmoid colon resected, as well as the adherent ileum. An end-to-end anastomosis was performed between the large bowel and the ileum.

The specimen obtained at the first operation consisted of 30 cm. of the ileum, the cecum, and 24 cm. of the ascending colon, together with adjacent fat and mesentery. In the region of the ileocecal valve an adenocarcinoma was found which extended proximally into the ileum for 6 cm. and involved the entire circumference of the ileum, narrowing the lumen to a diameter of 3 mm. The mucosal surface of the involved distal 6 cm. of the ileum was ulcerated. There was no gross deformity of the cecum. Lymph nodes contained metastatic tumor. The specimen obtained at the second operation consisted of sigmoid colon 18 cm. in length. Five cm. from the distal margin of the specimen was a 20 by 30 mm. ovoid lesion which was firm and slightly elevated above the surrounding mucosal surface. There was ulceration of the mucosal surface. Microscopic study revealed the presence of an adenocarcinoma which was continuous at the periphery with the adjacent colonic mucosa. This was considered to be a primary tumor of the sigmoid rather than a metastasis from the cecal carcinoma.

Comment: It is possible that this patient had three bleeding lesions occurring simultaneously, a peptic esophagitis, carcinoma of the cecum and bleeding internal hemorrhoids. The histological examination of the carcinoma of the sigmoid made it seem unlikely that this was a source of bleeding. The disappearance, for a time at least, of gross red blood from the feces following hemorrhoidectomy makes it at least a reasonable assumption that this was the cause of some of the bleeding. The lessened severity of the hypochromic anemia by repair of the hiatus hernia makes it likely that this was a source of bleeding. Finally, the direct evidence obtained by the Cantor tube leaves little doubt that there was bleeding in the region of the carcinoma of the cecum. The diagnosis of carcinoma of the cecum was unduly delayed in this patient by failure to repeat the barium enema at frequent intervals during the time it was obvious that bleeding lesions still existed. It might have been possible to have obtained more specific information about the relative importance of the bleeding lesions had radioactive chromium^{51} studies been carried out in conjunction with the Cantor tube.

CASE V. A thirty-five year old man was admitted to the N. I. H. on June 10, 1955, with a chief complaint of a progressive paralysis of the lower and upper extremities of six months' duration, and complete loss of hair. Six months before admission the patient noted the onset of weakness of the lower extremities which progressed so that he was unable to walk. Later his upper extremities also became involved in a symmetrical fashion so that by the time of admission he was unable to dress or feed himself or sit up in bed. The patient experienced an episode of hematemesis and tarry feces six months before admission and his referring physician found an active duodenal ulcer by an upper gastrointestinal x-ray. At this time he received thirteen blood transfusions. The patient denied any tarry feces or hematemesis since the original episode six months before admission.

Laboratory studies on admission showed a hematocrit of 31 per cent, reticulocyte count of 15 per cent, MCHC of 33 vol. per cent, and a negative Coombs' test. The red cells were normochromic on the stained blood smear. An admitting diagnosis of hemolytic anemia was made. A red cell survival study by the chromium^{51} technic was markedly short with disappearance of all but 10 per cent of the autotransfused labeled cells in twenty-five days. (Fig. 2.) Fecal occult blood tests were ordered on admission but none were obtained until ten days after admission, when two were positive. On the twenty-second day of the first chromium^{51} red cell survival study the chromium^{51} content of the stools was equivalent to 18 ml. of blood shed over a four-day period. (Fig. 2.) During this hospital stay the hematocrit rose to normal levels and the reticulocytes disappeared. A second chromium^{51} red cell survival study three months later (Fig. 2) was normal.

Comment: This case is an example of the ease with which gastrointestinal bleeding, stopped shortly after admission, can be confused with a hemolytic anemia. In this instance iron deficiency was not present so the anemia was normochromic and the patient was able to respond to acute blood loss with a reticulocytosis.

CASE VI. A seventy-four year old woman entered the Hitchcock Hospital with a chief complaint of severe shortness of breath for eight weeks. She had been in good health until eight weeks prior to admission when she experienced a copious, bloody diarrhea; however, she recalled that she had eaten many beets the day before she noted this red material in her feces. Seven weeks before admission she had had a similar episode of diarrhea but had not seen any material resembling blood. She denied the occurrence of tarry feces. She had been taking capsules of an unknown nature four times a day for one year for arthritic pains in the knees. She thought they contained

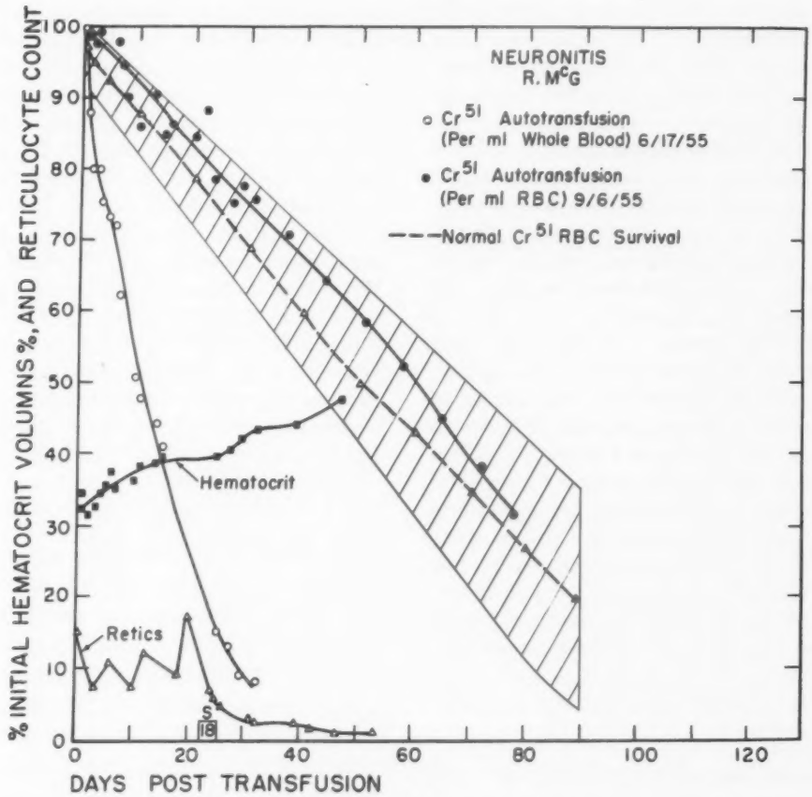

FIG. 2. Cr^{51} red cell survival in Case v. The cross hatched area defines the limits of normal Cr^{51} red blood survival corrected for elution [*1*]. The box with "S" above represents the ml. of blood present in the stool.

aspirin. She also was taking vitamin pills three times a day.

The admission laboratory findings included a white blood cell count of 2,000 per cu. mm. with a normal differential, a hemoglobin of 3.0 gm. per cent, and a hematocrit of 11 per cent. The red cells did not look hypochromic on the stained blood smear but there was considerable variation in their size and shape. A reticulocyte count was not taken on admission, but after four blood transfusions when the hemoglobin was still 8.5 gm. it was 0.1 per cent. During this time four consecutive stools were negative for occult blood and the next seven positive. The bone marrow was hypercellular but otherwise normal. There was a small amount of stainable iron in the marrow but the marrow aspiration was performed after the patient had received three transfusions. A diagnosis of marrow failure was made because of the absence of reticulocytosis and the presence of iron in the marrow. A bleeding lesion of the alimentary tract was also suspected because of the finding of occult blood in the feces. X-ray studies of the entire intestinal tract were within normal limits except for a diverticulum in the second portion of the duodenum. The barium enema was repeated and again was within normal limits. An esophagoscopy revealed no abnormalities. Sigmoidoscopy to 25 cm. revealed a polyp 3 mm. in diameter at 24 cm. which was fulgurated. A four-day stool collection made one week after sigmoidoscopy showed an excretion of 17 ml. of blood per day as measured by the chromium[51] technic. A Cantor tube was passed and as soon as the stomach was entered benzidine-positive material was obtained. After three hours the tube was removed and not allowed to progress through the gastrointestinal tract. Because of the finding of persistently benzidine-positive material in the stomach, a preoperative diagnosis of upper gastrointestinal bleeding was made.

At operation on April 2, 1956 the interior of the stomach and first and second portions of the duodenum appeared normal as viewed through a proctoscope passed into the first portion of the duodenum. The duodenal diverticulum could not be seen. Subtotal gastrectomy with a jejunogastrostomy was performed. The resected portion of the stomach and duodenal wall was normal both grossly and histologically. Thirty days after operation the stools continued to be positive for occult blood. During 400 postoperative days the patient has required sixty-six transfusions to maintain an average hemoglobin of 10 gm. per cent. On December 22, 1956 (eight months postoperatively), 1.3 ml., and from July 5 to 8 an

average of 2.5 ml. of whole blood per day were present in the feces as determined by Cr^{51}. A bone marrow obtained December 11, 1956, showed an increased amount of stainable iron. Failure to detect increased amounts of blood in the stool on two occasions following the operation, the finding of increased amounts of iron in the bone marrow, and the number of blood transfusions needed would suggest that the patient's anemia was caused by a combination of marrow failure and increased hemolysis. Barium enema, upper gastrointestinal series, and small bowel x-rays were repeated twelve months postoperatively with negative findings except for the gastric resection. Sigmoidoscopy at this time showed a small polyp in the sigmoid which was removed by electrocautery and diagnosed histologically as grade 1 adenocarcinoma. There was no ulceration or bleeding observed from the polyp. The behavior of the patient with respect to her need for blood transfusions after removal of this polyp was no different than before. The patient died seventeen months after operation following a massive myocardial infarction. Postmortem examination revealed a diverticulum of the duodenum, three small polyps in the large intestine, a well healed gastrojejunostomy, old and recent infarcts of the heart with thrombosis of the right and left coronary arteries and increased iron in the liver, spleen and bone marrow.

Comment: Possible interpretations to account for the lack of correlation between the laboratory findings of blood in the stools and the findings at operation are: (1) That no bleeding occurred in the stomach and that the blood obtained by the tube was caused by trauma incident to passage of the tube. Further information on this possibility would have been obtained if the tube had been allowed to pass through the intestine to the terminal ileum. If the bleeding had been caused by trauma, subsequent samples very likely would not have shown increased amounts of blood. Furthermore, allowing the tube to pass through the gut, despite the apparent positive findings in the stomach, might have disclosed a small bowel lesion. (2) That the patient really did bleed from the stomach from a small vessel which went undetected at operation and pathological examination. The first possibility seems more likely in view of the findings after operation and her subsequent course.

Case VII. A twenty year old male medical student in good health and with no complaints volunteered to drink 20 ml. of blood and was instructed to check his feces by the benzidine dihydrochloride test daily until they became negative. He reported that his feces as tested by himself remained positive (within fifteen seconds) for occult blood for seven days following the ingestion of the blood. The instructor of the course then tested the student's feces for seven additional days and found that five of the seven stools gave a positive result within fifteen seconds. Identical benzidine dihydrochloride and peroxide reagents were used by the rest of the class, all of whom reported negative tests three to four days after the ingestion of the blood. Laboratory data revealed a hemoglobin of 16 gm. per cent and a hematocrit of 47 per cent. Proctoscopy to 24 cm., barium enema, upper gastrointestinal and small bowel x-rays were within normal limits. Occult blood tests on a four-day fecal homogenate were positive within fifteen seconds, but Cr^{51} studies indicated only 1.5 ml. of blood per day in the stool. This figure is well within normal limits and the student was assured that there was no evidence of a blood losing lesion. One year following this episode the student has remained in good health and has not had any anemia.

Comment: The reason for the positive benzidine tests in this student is not known. He was eating the same diet (hospital cafeteria) as the other medical students. After the studies were finished it was found that he was taking multiple vitamin pills. The influence of the diet, or prior boiling of the feces, and the vitamins on the occult blood test in this patient could not be studied further because all these events occurred just before graduation. In this instance, the quantitation of the stool by the Cr^{51} technic for shed blood proved to be of great help in allowing the physician to assure the patient that there was no evidence for increased gastrointestinal blood loss.

Case VIII. Approximately four years prior to admission to the N. I. H., this sixty-five year old white man had the sudden onset of a syncopal episode, following the act of defecation. He was told that he had had an internal hemorrhage and was given 5 units of whole blood. Proctoscopic examination and gastrointestinal series were normal. He was given oral hematinics consisting of vitamin B_{12}, folic acid and iron which he had continued until admission. A blood count taken two years prior to admission was normal. About five months prior to admission a sensation of "stuffiness" of his nose, giddiness, and intermittent nausea developed. He was hospitalized because of anemia. A gastrointestinal series and barium enema were normal. Bone marrow aspirations were said to be normal. The feces were consistently positive for occult blood. He was given four units of whole blood. On admission to the N. I. H. the patient appeared to be chronically ill, with moderate pallor of the mucous membranes. The abdomen was soft, non-tender and no masses, liver or spleen, were palpable. The hemoglobin was 10.9 gm. per cent, hematocrit 34.5 per cent, reticulocytes 4.5 per cent, MCHC 32.0, MCV

88 μ^3, and MCH 27 μg. Seven specimens of feces were positive for occult blood. Two upper gastrointestinal series were normal. Proctoscopic examination to 22 cm. revealed external and internal hemorrhoids. Cr^{51} quantitative fecal blood measurements revealed 8.5 ml. of blood per day over a four-day period. Aspirated samples from a Cantor tube were consistently negative for occult blood until the distal third of the ileum was reached, at which time they became persistently positive. Small bowel x-ray studies after barium was instilled through the Cantor tube were considered normal. The mucosal pattern of the ileum was intact. Laparotomy was performed and a nodular mass about 2 inches in diameter was found in the distal ileum approximately 2 feet from the ileocecal valve. This was located in the mesenteric border of the ileum. There were numerous large blood vessels traversing its surface. The mass protruded into the lumen of the gut; however, there was no apparent obstruction. The mass and 6 inches of the distal ileum were resected and an end-to-end ileoileostomy was performed. The pathologic diagnosis of the specimen was acute ulceration of a leiomyoma in the terminal ileum. The patient was discharged and instructed to take oral ferrous sulfate. Six months later the hemoglobin was 16.7 per cent, hematocrit 47 per cent, reticulocytes 1.1 per cent, and the serum iron 134 μg. per cent.

Case IX. This fourteen year old white boy's illness dates back to early childhood. At three years of age his parents had noted that he was pallid and they were advised by a physician that he had iron deficiency anemia with a hemoglobin of 9.5 gm. per cent. There was a prompt favorable response to oral iron therapy both clinically and hematologically. This continued as long as iron was continued; however, as soon as it was discontinued hemoglobin levels fell to between 8 and 10 gm. per cent. At the age of seven years a diagnosis of iron deficiency anemia secondary to gastrointestinal bleeding of an occult nature was made because fecal examinations were consistently positive for occult blood and there was no evidence of blood loss from any other site. Gastrointestinal x-rays were normal and no sign of bleeding could be determined. At the age of nine years a diagnosis of a bleeding Meckel's diverticulum was entertained because of one episode of acute abdominal pain and intermittent vague abdominal complaints. At ten years of age he underwent an exploratory laparotomy with the removal of a Meckel's diverticulum and a normal appendix. However, following surgery feces were persistently positive for blood. An anemia with microcytic, hypochromic red cell indices developed each time iron therapy had been discontinued.

Physical examination on admission to the N. I. H. showed the spleen to be palpable 1 fingerbreadth below the left costal margin. The hemoglobin was 10.3 gm. per cent, hematocrit 33 per cent, MCH 26.5, MCHC 32, reticulocytes 1.0 per cent, serum iron 24 μg. per cent, and total iron-binding capacity 254 μg. per cent. Oral iron therapy was discontinued approximately ten days prior to admission. During the first several weeks of admission the hemoglobin fell to 6.6 gm. per cent, the MCHC to 28.5 gm. per cent, and the serum iron to 14 μg. per cent. Three fecal specimens were positive for occult blood. A proctoscopic examination, barium enema, upper gastrointestinal series, and small bowel series were normal. The patient was losing 60 ml. of whole blood daily during a seven-day period as measured by Cr^{51} technic. A Cantor tube was allowed to traverse the gut. Samples were negative for the presence of blood until the tube was in the proximal jejunum at which time samples became persistently positive. Barium was instilled at this point and abdominal fluoroscopy revealed no evidence of a lesion in the small bowel. Following this the patient underwent an exploratory laparotomy and a localized hemangioma of the proximal jejunum was resected. The patient was given oral iron for three months. Eight months following surgery the hemoglobin was 14 gm. per cent, hematocrit 47 ml. per cent, and reticulocytes 0.4 per cent.

COMMENTS

Apparent Blood Content of Normal Stool as Measured by Cr^{51}. The finding of the current study by the Cr^{51} technic of a loss of 1.2 ml. of whole blood per day from the normal human gastrointestinal tract agrees closely with 1.3 ml. found by Roche et al. [*4*].

Sensitivity of the Benzidine Dihydrochloride Test. The benzidine dihydrochloride test in the current study used a 3 per cent H_2O_2 solution rather than 0.6 per cent as described by Ham [*5*]. Ham [*5*] found a "3+" reaction with 15 mg. per cent hemoglobin in aqueous solution after one minute and that diluting hemoglobin with feces greatly reduced the sensitivity of the test. Needham and Simpson [*6*] found that the modified Gregerson test (benzidine dihydrochloride and barium peroxide) gave a positive reading in thirty seconds to a 0.3 mg. per cent solution of hemoglobin in water and a 30 mg. per cent suspension in feces. Hepler et al. [*7*] using the Ham filter paper test with 3 per cent H_2O_2 (identical to that used in the current study) found that 150 mg. per cent was the minimum concentration of hemoglobin in feces to result in a positive benzidine dihydrochloride filter paper test in one minute. The finding in the current study of a positive benzidine dihydrochloride filter paper test after one minute to 2.5 mg. per cent and 300 mg. per cent in aqueous and fecal dilutions respectively is in agreement

with Hepler and, with allowance for difference in methods, those of Ham and Needham.

Recovery of Radioactivity from Feces after Oral Ingestion of Cr^{51} Labeled Red Blood Cells. Owen et al. [*8*] found that Cr^{51} fed to two dogs as Cr^{51} labeled red blood cells was quantitatively recovered in the feces, which agrees with the finding in the current study that 99 ± 10 per cent of Cr^{51} fed to ten humans was recovered in the feces. Owen [*8*] found that one-third of Cr^{51} fed as $Na_2Cr^{51}O_4$ in aqueous solution was absorbed from the gastrointestinal tract of one dog and two rats. This finding is in contrast to our finding that less than 4 per cent of the $Na_2Cr^{51}O_4$ diluted with grape juice was absorbed by two human subjects.

Use of Cr^{51} and Fe^{59} to Quantitate Gastrointestinal Blood Loss. Cooper et al. [*9*] and Bannerman [*10*] and Roche [*4*] have reported the use of the Cr^{51} for quantitating blood loss in patients with gastrointestinal lesions.

The use of radioactive Fe^{59} to measure gastrointestinal blood loss in hookworm disease has been reported by Hahn and Offutt [*11*] and Gerritsen et al. [*12*]. Callender et al. [*13*] have found that 11 per cent of rabbit hemoglobin biologically tagged with Fe^{59} is absorbed from the normal human gastrointestinal tract and 22 per cent by the iron deficient human. Since biologically labeled Fe^{59} red blood cells from a homologous donor would have to be injected intravenously or, if the patient is injected intravenously with Fe^{59}, one must wait approximately two weeks before blood loss can be quantitated, the use of this isotope is not as practical as Cr^{51} for quantitating gastrointestinal blood loss.

The most important factor in the correct diagnosis of chronic gastrointestinal blood loss is a high index of suspicion on the part of the physician, even in the face of clinical and laboratory findings which appear to "rule out" chronic blood loss as a cause of the anemia. In cases in which the bleeding has been of sufficient magnitude to result in iron deficiency anemia, the finding of hypochromia of the red cells, the absence of stainable iron in the bone marrow, a low serum iron, a response to iron therapy and positive chemical tests for occult blood in the feces, will usually lead to the correct diagnosis. The feces may be negative for occult blood in patients with chronic gastrointestinal blood loss, because of either intermittent bleeding or inadequate sampling of the stool. Of the two possibilities, intermittent bleeding is the far more common. In patients with an obscure anemia and no history of blood loss, quantitation of the amount of blood in ml. per day lost in the stools by the radioactive Cr^{51} technic has been an aid in establishing the presence of hemorrhage. Data have been presented to show that the Cr^{51} technic is a reliable measure of the maximum amount of blood shed into the gastrointestinal tract.

Once it has been established that a bleeding lesion exists in the bowel the physician is obligated to find the source of the gastrointestinal bleeding. This usually can be done by x-ray and endoscopic studies. In Cases II, III, VIII and IX in this study in which x-ray and endoscopic studies did not lead to a localization of the lesion, or in instances such as Case IV in which more than one bleeding gastrointestinal lesion was demonstrated, frequent sampling of the intestinal contents through a Cantor or Miller-Abbott tube as it passes through the gastrointestinal tract may lead to localization of the lesion. Of course, the success of such a test rests on the premise that the patient is bleeding from the intestinal lesion at the time of study.

In rare instances quantitation of gastrointestinal blood loss by Cr^{51} can erase the suspicion of a bleeding lesion of the bowel caused by false positive chemical occult blood tests (Case VII).

The major disadvantage of this test is the necessity of a rather lengthy technic involving the administration of Cr^{51} tagged red cells to the patient. A far more useful test would be a chemical test capable of quantitating in ml. per day the amount of blood present in the stool.

The indiscriminate use of iron therapy in cases of chronic blood loss is dangerous to the welfare of the patient in that it usually delays the detection and treatment of the bleeding lesion (Cases II and IV). In some instances in which complete laboratory and x-ray studies fail to clarify the cause of the anemia, a six weeks' trial of iron therapy can be considered a logical procedure, if adequate follow-up of the patient is assumed. Frequent tests should be performed on the feces for occult blood during this interval of time. The benzidine dihydrochloride test does not give a positive test for iron in the feces [*6,14,15*]. At the end of this six weeks' period iron should be discontinued. If the hemoglobin has not returned to normal and the reticulocyte count is not elevated, chronic blood loss as the sole cause of the anemia has been ruled out.

If the anemia has responded to iron therapy, then the existence of a chronic bleeding lesion, past or present, has been established, and persistent efforts should be made to detect the lesion by adequate follow-up studies.

SUMMARY

1. A method for quantitating the amount of blood lost in the feces by means of erythrocytes labeled with radioactive sodium chromate is described. The maximum amount of blood lost by normal subjects is 1.2 ± 0.5 ml., with a range of 0.3 to 2.0 ml. of whole blood per day.

2. The sensitivity of the qualitative benzidine dihydrochloride test to hemoglobin in aqueous solution has been compared with the sensitivity to hemoglobin in homogenized stools. It was found that the sensitivity of the test was approximately 100 times greater for hemoglobin in aqueous solution than for hemoglobin present in the stools.

3. The use of the Cr^{51} technic for quantitating blood loss from the gastrointestinal tract, combined with intestinal intubation for localizing the level of bleeding, has been tested in nine cases in which there was difficulty either in establishing that the anemia was due to blood loss or in localizing the level of bleeding by x-ray studies. In eight of the nine cases these technics were of aid in arriving at the correct diagnosis. In one case the interpretation of the Cr^{51} and intubation data was not substantiated by the findings at operation.

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Polycythemia and Renal Carcinoma*

Report of Ten New Cases, Two with Long Hematologic Remission Following Nephrectomy

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THE coexistence of polycythemia and carcinoma of the kidney has been reported in at least twenty-one patients to date [*1–12*]. Although the first notation [*1*] we have encountered appears in the American literature, and eight of the cases thus far have occurred in this country, American observers have merely stated the fact of association. Detailed accounts have been presented by Medvei [*2*] (Austria), Fairley [*3*] (Australia), Forssell [*4,5*] (Finland), Videbaek [*6*] (Denmark), Gros [*9*] (Germany), Moe [*10*] (Norway), and Herbeuval [*11*] (France). Personal communications from several clinics suggest that the syndrome is more common than the relatively few published reports would indicate. In addition, consideration of the association of polycythemia with renal neoplasms may elucidate important mechanisms in normal and abnormal hematopoiesis. Ten additional cases are recorded and compared with the findings of others.

SUBJECTS AND CRITERIA

Nine of our patients, seven men and two women, represent 4.4 per cent of 205 patients with "primary" polycythemia who were seen at the Presbyterian Hospital between 1936 and 1957, and 2.6 per cent of some 350 instances of carcinoma of the renal parenchyma between 1929 and 1957. Our tenth patient, a male, was encountered elsewhere in consultation. Criteria for the diagnosis of polycythemia consisted of elevation of hemoglobin to a minimum of 18.0 gm. per cent, red blood cells to at least 6.3 million per cu. mm., and hematocrit to a minimum of 55 per cent. (These criteria would exclude two of Forssell's four cases.) For the diagnosis of renal carcinoma, tissue for examination was available from six patients. In the other four, clinical and radiographic evidence of renal neoplasm was deemed conclusive. We have excluded one male patient with polycythemia and bronchogenic carcinoma metastatic to brain and kidney, and two other patients with polycythemia, hematuria and a mass in the flank (presumably renal), both of whom lacked definitive radiographic studies of the urinary tract. These three patients may well have had the syndrome but the evidence is considered insufficient to warrant their inclusion.

We have also discarded two cases from the literature, one of Fairley's [*3*], with polycythemia and oat cell carcinoma of the lung, metastatic to both kidneys and elsewhere; and the patient of De Marsh and Warmington [*13*], in whom polycythemia, secondary to a benign renal adenoma, disappeared for five years following nephrectomy.

CASE 1. I. B. (No. 296983), a forty-nine year old Russian-born Jewish bartender, was first seen in 1922 because of precordial pains of recent onset. He was found to have polycythemia vera, with normal blood pressure; hemoglobin, 22.4 gm. per cent; red blood cells, 6.6 million per cu. mm.; and white blood cells, 7,900 per cu. mm. with 84 per cent neutrophils; an enlarged heart with electrocardiographic changes strongly suggesting myocardial damage; and a spleen enlarged to the umbilicus. He was treated with

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segmental radiation to the entire body, over an eight-month period, and the hemoglobin and red cells returned to normal levels; there was a great reduction in the size of the spleen and symptomatic relief.

In July, 1926, he had returned complaining of occasional episodes of painless hematuria and of itching of the skin when wet during the three-year interval. His spleen had enlarged to 3 cm. below the costal margin, hemoglobin was 20.5 gm. per cent; red blood cells, 6.6 million per cu. mm.; and white blood cells, 8,100 per cu. mm. with 83 per cent neutrophils. Painless hematuria had continued intermittently for the next three months, and in October, 1926, he was admitted with a splenic infarction. Both liver and spleen were enlarged; hemoglobin was 19.9 gm. per cent; red blood cells, 7.4 and 8.1 million per cu. mm.; and white blood cells, 15,000 and 10,000 per cu. mm. Hematuria was attributed to renal infarction. The kidneys were not palpable, and x-ray films showed no urinary stones or abnormality of the right renal outline; the left was not seen distinctly. A gastrointestinal series was normal. He was discharged in a week without specific therapy.

Three months later, painless hematuria had recurred and had persisted intermittently for the next two years. In April, 1929, his liver was not felt; the spleen had enlarged to 13 cm. below the costal margin, and the left kidney was palpable for the first time, remaining so subsequently. His hemoglobin was 18.4 and 21.5 gm. per cent; red blood cells, 9.7 and 9.2 million; and white blood cells, 13,100 and 14,500 per cu. mm. with 87 per cent neutrophils. Following phenylhydrazine therapy, the hematologic findings did not change over a four-year period. A single platelet count in 1931 was 437,000 per cu. mm.

In 1933, gout developed, and he was hospitalized elsewhere from March 17, 1934, to January 9, 1935. Physical and hematologic findings were as before; the urine showed 1 plus to 3 plus albumin but was otherwise normal. X-ray films of the chest showed normal lungs. His blood volume, by the vital-red method, was 144 cc./kg. body weight (normal, 78 to 97) [*30*]; plasma volume, 55 cc./kg. (normal, 42 to 56); red blood cell volume, 89 cc./kg. (normal, 27 to 37); and hematocrit, 63 per cent. The serum uric acid ranged from 6.2 to 6.7 mg. per cent between attacks of gout, and from 9.0 to 10.4 mg. per cent during an acute attack. The basal metabolic rate varied between +11 per cent and +18 per cent. The serum cholesterol was 91 mg.; calcium, 10.6 to 12.1 mg.; and phosphorus, 4.4 mg. per 100 cc. During this hospitalization, a basal cell epithelioma was removed.

After six months at home, mainly in bed, with several gouty attacks, he was readmitted elsewhere on July 11, 1935. Physical and laboratory findings were as before. Phlebotomy was performed twice, with removal of 500 cc. of blood each time. In May, 1936, a moderate pleural effusion developed of specific gravity 1.012 and containing 3,400 red blood cells per cu. mm. No tumor cells were found, and smear, culture and guinea-pig inoculation were negative for tubercle bacilli. After a month of fever, anemia and increasing weakness, he died on August 30, 1936. The autopsy diagnoses were gout, adenocarcinoma of the right kidney (total weight 330 gm.) metastatic to the left kidney (total weight 270 gm.), right pyelonephritis with abscess formation, bilateral nephrolithiasis (gravel), generalized arteriosclerosis, coronary atherosclerosis, myocardial fibrosis, scrotal hernia, benign prostatic hypertrophy, and miliary tuberculosis of lungs, liver, spleen, intestine, adrenals and kidneys. Microscopic examination of the renal neoplasm showed a papillary cystadenocarcinoma.

Comment: Undoubted polycythemia vera was present in this, the only patient in our series with marked splenomegaly and leukocytosis. The painless hematuria beginning a few years after the polycythemia may, in retrospect, have been due to a slowly growing left renal tumor rather than to polycythemia-induced renal infarction.

Case II. J. P. (No. 521960), a forty year old American-born steamfitter of Italian descent, was admitted in August, 1937, for investigation of lumbosacral pain of four months' duration associated with a twenty-four pound weight loss. The past medical history and system review were negative, except for a recent increase in his chronic "cigarette" cough. On physical examination, the patient appeared chronically ill, with considerable pain in the back and a purulent cough. He had a blood pressure of 130/70 mm. Hg, suffused conjunctivas, and plethora. There were no abnormal physical findings other than a few moist rales at both lung bases.

Laboratory data included hemoglobin, 22.5 gm. per cent; red blood cells, 8.0 million per cu. mm.; white blood cells, 7,200 per cu. mm. with normal differential, platelets 198,000 per cu. mm., reticulocytes 2 per cent, and erythrocyte sedimentation rate 2 mm./hour. Repeated urinalyses showed 0 to 1 plus protein and rare red blood cells. A chest x-ray film showed bilateral hilar enlargement with some exaggerated bronchovascular markings, but a bronchogram was considered to be normal. Skeletal radiographic survey disclosed osteolytic lesions of several vertebrae and a rib. Gastrointestinal series and barium enema were normal, but an intravenous pyelogram showed complete distortion of the right renal pelvis and calyces by a mass containing areas of calcification, presumably a renal neoplasm.

Other laboratory data included an arterial oxygen saturation of 90 per cent with the patient at rest; serum albumin, 3.9 gm.; globulins, 2.3 gm.; calcium, 13.5 mg.; phosphorus, 2.7 mg.; alkaline phosphatase, 5.6 Bodansky units; cholesterol, 147 mg.; and nonprotein nitrogen, 32 mg. per 100 cc. The basal metabolic rate was plus 27 per cent. Sputum culture

was negative for tubercle bacilli. No urinary Bence Jones protein was found.

He was treated for six weeks with palliative radiation to the lumbar spine, since surgery for the presumed renal neoplasm was believed to be contraindicated in the presence of bony and mediastinal node metastases. For terminal care he was therefore transferred elsewhere in October. At that time a mass in the right flank was palpable, and retrograde pyelography disclosed a right renal tumor. His hemoglobin level had fallen to 85 per cent; red blood cells, 4.7 million per cu. mm.; and white cells, 15,200 per cu. mm. He died on November 3, 1937; an autopsy was not performed.

Comment: Asymptomatic polycythemia, without leukocytosis, thrombocytosis or splenomegaly, was detected during the course of evaluating a renal tumor, probably hypernephroma. The normal arterial oxygen saturation rules out a cardiorespiratory basis for secondary polycythemia.

Case III. R. H. (No. 849189), a fifty-nine year old Swedish-born minister, was admitted on November 13, 1946, complaining of pain in the upper part of the abdomen, of two month's duration. There had been no urinary or other symptoms, but an intravenous pyelogram a few days before admission showed a cyst or tumor of the right kidney.

The physical findings included a blood pressure of 164/82 mm. Hg, conjunctival suffusion, and a poorly defined mass in the right upper quadrant of the abdomen. The spleen was not palpable, and the prostate was minimally enlarged. The hemoglobin was 20 gm. per cent; red blood cells, 8.2 million per cu. mm.; and white blood cells, 9,050 per cu. mm., with a normal differential count, and platelets 202,000 per cu. mm. The urine had a specific gravity of 1.012 and contained no albumin or glucose, but occasional red and 5 to 10 white blood cells. The blood urea nitrogen was 11 mg. and the fasting blood sugar was 122 mg. per 100 cc. With the patient at rest, the arterial blood had an oxygen saturation of 92.0 per cent. Heart and lungs were normal on radiographic examination, and an intravenous pyelogram suggested right renal tumor.

On November 22, 1946, a right nephrectomy was performed. A well encapsulated tumor was found, involving the greater part of the right kidney. The total weight of the specimen was 522 gm. and the microscopic diagnosis was clear cell carcinoma.

After an uneventful postoperative course, the patient was discharged on December 11, 1946, without further hematological studies. In July, 1955, he was well and active, with values for hemoglobin of 14.0 gm. per cent; red blood cells, 4.7 million per cu. mm.; and white cells, 7,900 per cu. mm., with a normal differential count. In July, 1956, and 1957, his blood values were similarly normal.

Comment: The temporal relationship of the polycythemia and the renal tumor is uncertain, but the two conditions apparently developed concurrently. The eleven-year hematologic remission after nephrectomy and without other therapy for polycythemia is noteworthy. His current good health and normal peripheral blood picture rule out myeloid metaplasia or leukemia.

Case IV. H. S. (No. 933845), a fifty-four year old Polish-born Jewish restaurant manager, was admitted in December, 1948, because of a mass in the left side of the abdomen known to have been present for the preceding eight months. His health had been excellent, except for a brief episode of pain in the chest at the age of forty-five years, which had not recurred; dyspnea and orthopnea were denied, and yearly electrocardiograms had remained normal. Eight months before admission his physician had discovered a mass in the upper left quadrant of the abdomen. The patient had thereupon consulted many other physicians, several of whom recommended surgical removal of the mass. This he had declined, despite anorexia, a thirty pound weight loss, and progressive weakness.

In November, 1948, a month before admission, polycythemia vera was diagnosed on the basis of the following laboratory data: hemoglobin, 125 per cent; red blood cells, 7.4 million per cu. mm.; white blood cells, 5,300 per cu. mm.; and platelets, 280,000 per cu. mm., hematocrit, 67 per cent; and reticulocytes, 2 per cent. The bone marrow showed no abnormalities and was considered compatible with polycythemia vera. The mass in the abdomen was interpreted as an enlarged spleen and a therapeutic course of radioactive phosphorus was advised.

However, one week later, roentgenograms of the abdomen showed a huge mass, which contained faint calcific speckling and occupied almost entirely the left posterior portion of the abdomen. An intravenous pyelogram showed a normal right kidney and a left renal tumor with calcifications.

Physical examination on admission showed a chronically ill appearing man, with a blood pressure of 150/80 mm. Hg and a large hard irregular mass in the left upper abdominal quadrant. Laboratory data showed hemoglobin, 125 per cent; red blood cells, 5.9 million per cu. mm.; and white blood cells, 7,000 per cu. mm. The urine contained a trace of albumin and rare red blood cells. The blood urea nitrogen, fasting blood sugar, Kline test and electrocardiogram were normal. A chest x-ray film showed multiple areas of increased density throughout both lung fields, mostly well rounded and discrete, principally involving the lower lobe of the left lung, and compatible with metastatic carcinoma.

With the discovery of metastatic nodules in the lungs, it was decided to treat the left kidney with radiotherapy rather than to attempt surgical excision

of the tumor. He received such treatment as an out-patient but bony metastases developed and the patient died.

Comment: The polycythemia apparently developed in association with a huge, partially calcified renal tumor. There was no splenomegaly, leukocytosis or thrombocytosis. The presence of metastatic pulmonary disease raises the theoretical possibility of secondary polycythemia, but this is unlikely in the absence of clinical pulmonary symptoms or cyanosis. Unfortunately, an arterial oxygen saturation was not obtained.

CASE V. B. C. (No. 993231), a sixty-seven year old Russian-born Jewish widow, was admitted on April 5, 1950, because of twenty-four hours of bloody urine. In 1938, a left radical mastectomy had been performed elsewhere for carcinoma, with no evidence of recurrence or metastasis during careful follow-up in the interval. She had been overweight for many years and hypertensive for two years, with systolic pressures around 180 mm. Hg. She had had mild exertional dyspnea, but no other cardiorespiratory symptoms.

Several days before admission, she had pain in the left flank which was followed by gross hematuria. Positive physical findings included a blood pressure of 180/112 mm. Hg, cyanotic lips, obesity, moderate cardiac enlargement, a liver palpable two fingerbreadths below the costal margin, and a firm mass in the left flank.

Laboratory data included hemoglobin values between 17.4 and 19.0 gm. per cent, red blood cells between 6.2 and 7.2 million per cu. mm. and white cells between 7,800 to 9,700 per cu. mm., with a normal differential count; hematocrit, 63.0 to 66.1 per cent; and platelets, 184,000 and 192,000 per cu. mm. The urine was bloody on gross examination with no sugar or albumin. Normal values were obtained for venous pressure, clotting time, bleeding time, prothrombin time and plasma proteins. The blood urea nitrogen was 15 mg. and the uric acid was 5 mg. per cent; serum CO_2 was 47 volumes per cent. X-ray films showed a minimally enlarged heart and mild pulmonary congestion, cholelithiasis, a probable left renal tumor mass, and no evidence of bony metastases. The electrocardiogram indicated myocardial disease. Blood volume by the Evans blue technic, determined after a five pound weight loss on cardiotonic therapy, was 8,670 cc., or 102 cc./kg. (normal 81 $\pm$ 10) [27]; plasma volume, 3,000 cc. or 35.4 cc./kg. (normal, 45 $\pm$ 5); red cell volume, 5,670 cc. or 67 cc./kg. (normal, 36); hematocrit, 65.4 per cent.

After phlebotomy was carried out, with removal of 400 cc. of blood, left nephrectomy was performed on April 28, 1950. A large renal tumor had extended to the perirenal fat and adjacent peritoneum, jejunum and regional lymph nodes. The total weight of the specimen was 434 gm. and the microscopic examination revealed a clear and granular cell carcinoma of the kidney with invasion of blood vessels and extension to fat and peritoneum. Calcific deposits were seen within the tumor. During the operation the patient received 1,000 cc. of blood as replacement. Postoperatively, she had thrombophlebitis, and a pulmonary embolus developed, but this responded to anticoagulants. Her blood counts were within normal limits, *viz.*, hemoglobin, 14.5 and 13.4 gm. per cent; red blood cells, 4.9 and 5.4 million per cu. mm.; and hematocrit, 45 per cent.

After her discharge from the hospital on May 31, 1950, she was seen as an out-patient during the next two months. Pulmonary and pleural metastases developed, and she died at home on August 13, 1950. Postmortem examination was not performed.

Comment: The polycythemia, without leukocytosis, thrombocytosis or enlarged spleen, was apparently not due to anoxia, judging from the minimal pulmonary congestion initially and the normal blood values three months later when pulmonary metastases appeared. The available data give no indication of the relative time of onset of polycythemia and renal carcinoma, but both were present when the patient was first seen. Following removal of the renal neoplasm her polycythemia disappeared. As she died four months postoperatively, however, the period of observation was too short to classify this case as a real remission of polycythemia.

CASE VI. S. G. (No. 125963), a seventy-two year old Polish-born Jewish weaver, was first seen on February 20, 1953, because of paresthesias of the toes of two months duration. He had been well, except for many years of symptoms referable to prostatic hypertrophy, until March, 1951, when a prostatectomy was performed at the Beth Israel Hospital, New York. Save for a blood pressure of 200/110 mm. Hg, preoperative physical examination was normal. Urinalysis showed white blood cells in the sediment but was otherwise negative. Hemoglobin was 17 gm. per cent; red blood cells, 5.7 million per cu. mm.; and white blood cells, 9,700 per cu. mm., with 69 per cent neutrophils and 29 per cent lymphocytes. The serum non-protein nitrogen was 33 mg. per cent. Pathologic examination disclosed prostatic calculi and benign hypertrophy. Copious bleeding from the prostatic fossa led to blood coagulability tests, all of which were normal—bleeding time, clotting time, prothrombin time, capillary fragility and platelet count (325,000 per cu. mm.). After transfusion with 1,000 cc. of whole blood, the patient made an uneventful recovery and was discharged on April 24, 1951.

He was readmitted to the Beth Israel Hospital on July 30, 1952, because of hematuria of three months' duration. His blood pressure was 150/88 mm. Hg;

the liver was palpable one fingerbreadth below the costal margin, but spleen and kidneys were not felt. X-ray films showed normal lungs and minimal cardiac enlargement. Hemoglobin was 18 gm. per cent; red blood cells, 6.2 million per cu. mm.; white blood cells, 15,300 per cu. mm., with 80 per cent neutrophils, 14 per cent lymphocytes; and platelets, 370,000 per cu. mm.; hematocrit was 60 per cent. Urinalysis showed 2 plus albumin, 6 to 12 red blood cells, and 6 to 10 white blood cells. On aspiration, the bone marrow appeared highly active, with normal cellular distribution and no abnormal forms. A hematologist diagnosed "unquestioned polycythemia." After urologic study disclosed a left renal mass, nephrectomy was performed. The microscopic studies revealed a clear cell carcinoma of the kidney. Again, continued postoperative blood loss led to transfusion of 1,500 cc. of whole blood. He was discharged on August 16, 1952.

When seen in the Presbyterian Hospital Clinic on February 20, 1953, he was plethoric and cyanotic, with a blood pressure of 180/110 mm. Hg. The liver was barely palpable, the spleen questionably so. There was no albuminuria or glycosuria. The hemoglobin was 18.1 and 18.6 gm. per cent; red blood cells, 6.4 million per cu. mm.; and white blood cells, 9,400 per cu. mm. A month later, corresponding values were 16.6 gm. per cent, 5.7 million per cu. mm., and 14,300 per cu. mm., with 78 per cent neutrophils. A single platelet count was 200,000 per cu. mm. The serum uric acid was 6.1 mg.; blood urea nitrogen, 19 mg.; and acid phosphatase, 4.1 and 2.2 mg. per cent. Vital capacity was 3.5 L. (83 per cent of normal), and I^{131} uptake 41 per cent. Abdominal films suggested splenomegaly to two radiologists.

The borderline hematologic findings and minimal symptoms were considered to warrant expectant therapy only. Chronic pyelonephritis and uremia developed gradually, and the patient was hospitalized twice at the Beth Israel Hospital, from April 17, to May 1, and from November 16, to December 2, 1955. On both admissions, his blood pressure was elevated to 220/110 mm. Hg, his heart was moderately enlarged, and no abdominal organs were palpable. With advancing renal impairment, the hemoglobin fell from 11.2 to 9.8 gm. per cent, red blood cells from 3.9 to 3.6 million per cu. mm., and hematocrit from 36 per cent to 30 per cent. The white blood cells numbered 12,500 and 21,000 per cu. mm. on the two admissions, with marked polymorphonuclear predominance. Both times, the patient responded to fluid and antibiotic therapy, and his leukocyte counts fell to 6,400 and 13,300 per cu. mm., respectively, with more nearly normal differential counts. However, his serum non-protein nitrogen rose from 71 mg. per cent on his first hospital discharge, to 118 mg. per cent on his second. No obstruction was found in his right kidney or ureter, and no evidence of metastatic carcinoma.

He died in December, 1955, presumably of uremia. Autopsy was not performed.

Comment: Polycythemia, first documented at the time of nephrectomy for renal clear cell carcinoma, was characterized by normal leukocyte and platelet counts, a single borderline serum uric acid value, possible splenic enlargement, and normal respiratory function. Massive operative blood loss hampered the diagnosis and, together with uremia, obscured the course of his polycythemia after nephrectomy. All that can be said is that eight months after nephrectomy, when the patient was not yet uremic and showed no convincing evidence for myeloid metaplasia or fibrosis, his hemoglobin and red cell count were within normal limits.

Case VII. C. S. (No. 182429), a seventy year old white retired man of Norwegian parentage, was admitted on April 30, 1954, for investigation of a mass in the right flank. He had been in excellent health until two months before, when he noted severe lumbar pain radiating to his left leg. This was associated with anorexia and moderate weight loss. Two days before admission gross hematuria developed and the patient consulted his physician who felt a mass in the right flank and found the patient's urine to contain 2 plus proteinuria and many red blood cells. An x-ray film of the lumbar spine showed an osteolytic lesion in the fourth lumbar vertebra.

On admission, positive findings included a hard, tender, ballotable spheroidal mass, 25 cm. in diameter, in the right upper quadrant of the abdomen, which moved with respiration. The prostate was slightly enlarged, but soft and smooth. The patient was not cyanotic, dyspneic or orthopneic; his fingers were not clubbed. Laboratory values included hemoglobin, 18.7 gm. per cent; red blood cells, 6.2 million per cu. mm.; and normal white blood cell and differential counts. Urinalysis showed 2 plus proteinuria and 3 to 5 red blood cells per high power field. The alkaline phosphatase was 6.6 Bodansky units; acid phosphatase, 2.9 Gutman units; albumin, 4.2 gm.; globulin, 2.8 gm.; and blood urea nitrogen, 12 mg. per cent. A stool guaiac test was negative. X-ray films of the lumbosacral spine demonstrated osteolytic lesions in the fourth and fifth lumbar vertebrae. An intravenous pyelogram showed a normal left kidney, but an enlarged right kidney with only scattered collections of contrast medium seen after seventy-five minutes. These findings were interpreted as indicating a right renal tumor.

Because of bony metastases, the renal tumor was considered inoperable, and the patient was treated with radiation to the lumbar spine. Two months later, in July, 1954, he again noted gross hematuria, and was readmitted to the hospital with urinary retention.

At this time, the hemoglobin was 18.9 gm. per cent; red blood cells, 6.3 million per cu. mm.; with a normal white count and differential. With bladder irrigation and removal of blood clots, he was able to void, and another course of radiotherapy to the right renal area was begun.

The patient was readmitted for the third time in August, 1954, following two massive hematemeses and associated melena. Despite considerable blood loss, his hemoglobin on admission was 17.0 gm. per cent, and the hematocrit was 43.1 per cent. Platelet count, venous clotting time and prothrombin time were all normal, but a gastrointestinal series showed a large peptic ulcer of the prepyloric antrum, on the lesser curvature, which appeared to be radiographically benign. A roentgenogram of the chest disclosed numerous discrete densities bilaterally, representing metastatic pulmonary disease. Gastrointestinal bleeding ceased following the institution of an antiulcer regimen and blood replacement.

After discharge, however, weight loss, anorexia and pain in the back became more severe, and the patient died in September, 1954. Autopsy was not performed.

Comment: Elevated hemoglobin and erythrocyte levels occurred in an elderly man with a far advanced renal neoplasm, with extensive osseous (and later pulmonary) metastases. Leukocytosis, thrombocytosis or splenomegaly were never noted. There was no apparent cause for a secondary polycythemia other than the renal tumor.

Case VIII. J. K. (No. 239456), a fifty-nine year old Latvian-born janitor, was first seen in July, 1955. He had been referred by his private physician for recently discovered polycythemia. Until 1948 he had been well, except for bilateral macular degeneration, gradual in progression, beginning in 1945. In 1948 he had had an episode of pain in the left flank, preceded by hematuria. He was unaware of passing a calculus, and an x-ray film taken in 1949 showed no stones. In 1951 a pre-emigration physical examination disclosed a mass in the left upper quadrant, and an intravenous pyelogram was said to show "pyelitis." On later review (1955) these films were interpreted as showing a left renal tumor, with mottling calcification.

Except for a slowly increasing facial ruddiness for several months, the patient had been well until June, 1955, when he had had a mild sore throat. A blood count showed his hemoglobin to be 21 gm. per cent; hematocrit, 74 per cent; red blood cells, 9.0 million per cu. mm.; and white cells, 8,200 per cu. mm., with a normal differential; and platelets 140,000 per cu. mm. The bone marrow was markedly increased in cellularity, with normal megakaryocytes and a normal differential count. A consulting hematologist diagnosed polycythemia vera and administered 4 millicuries of P^{32} orally on June 10, 1955. A month later, the complete blood count was virtually unchanged, and the patient was referred for further therapy.

Physical examination showed him to be plethoric, with conjunctival suffusion and engorgement of small vessels. The blood pressure was 120/80 mm. Hg. Other positive findings included moderate bilateral macular degeneration, and a mass in the left upper quadrant of the abdomen. Heart and lungs were normal; the liver and spleen were not palpable. Laboratory examination showed hemoglobin of 23.2 gm. per cent; hematocrit, 73.2 per cent; red blood cells, 7.8 million per cu. mm.; and white cells, 7,500 per cu. mm., with a normal differential count. Urinalysis showed no glucose, albumin or red blood cells. An upper abdominal radiograph disclosed a normal liver and spleen but a probable left renal tumor, partially calcified; urographic studies, including an aortogram, were confirmatory.

On August 30, 1955, on admission for nephrectomy, his complete blood count, including platelets, was unchanged. The reticulocytes numbered 1.4 per cent. Unfortunately, arterial oxygen was not measured at this time. His urinary sediment contained rare red and occasional white blood cells. Phenosulphonphthalein excretion was 90 per cent in two hours; serum urea nitrogen was 22 mg.; uric acid, 4.8 mg.; bilirubin, trace; calcium, 9.9 mg.; phosphorus, 3.0 mg.; and alkaline phosphatase, 2.3 Bodansky units per cent. An electrocardiogram was normal. An x-ray film of the chest was normal except for perihilar calcifications interpreted as old tuberculosis; a skeletal radiographic survey showed no bony disease.

Preoperative phlebotomy was performed four times with removal of a total of 2,000 cc. of blood in a week, and a resulting fall in hematocrit from 69.6 per cent on admission to 50 per cent prior to surgery. On September 25, 1955, a left nephrectomy was performed with removal of a clear cell carcinoma, which showed hemorrhages, fibrosis, hyalinization and calcification. The tumor had replaced approximately three-fourths of the kidney and weighed 524 gm. The spleen, palpated during the operation, was somewhat enlarged and firm. The estimated blood loss was 300 cc., and postoperative blood values varied within normal limits, hemoglobins ranging between 13.9 and 16.0 gm. per cent and hematocrit around 46 per cent. For persistent and complete prostatic obstruction, a retropubic prostatectomy was performed on October 10, 1955, with a pathological diagnosis of fibroadenoma and focal suppurative prostatitis. The blood loss was estimated at 750 cc., and 1,500 cc. of whole blood was transfused. For the next five postoperative days, hemorrhage from the prostatic bed resulted in a fall in hemoglobin to 8.8 gm. per cent, and in hematocrit to 30 per cent. During the postoperative course he received an additional transfusion of 1,500 cc. of whole blood with gradual cessation of bleeding. After three weeks of therapy with oral ferrous sulfate, he was discharged on Novem-

ber 1, 1955, feeling well and with a hemoglobin of 13.2 gm. per cent and a hematocrit of 37 per cent.

During the twenty-four months following nephrectomy, he has remained well and symptom-free, working full time as a janitor. His weight has been stable, he is no longer plethoric. Repeated physical examinations have been within normal limits, as have serial chest films, urinalyses, and determinations of blood urea nitrogen, alkaline phosphatase and erythrocyte sedimentation rate. He has maintained hemoglobin values between 12.9 and 14.4 gm. per cent and red cell counts between 3.4 and 4.7 million per cu. mm.; white blood cells and platelet counts have likewise remained normal. Bone marrow aspiration performed two months after nephrectomy showed moderate erythroid hyperplasia, and an arterial oxygen saturation on June 5, 1957, was 98.4 per cent with the patient at rest and 97.1 per cent with the patient exercising.

Comment: The malignancy of the kidney was certainly present in 1951 and possibly even in 1948. The polycythemia cannot be dated precisely, but the lack of symptoms and approximate onset of plethora in 1955 suggests that polycythemia began in 1955 or at the earliest in 1954. None of the usual cardiorespiratory or endocrine causes for secondary polycythemia were present. The polycythemia was characterized by absence of leukocytosis, thrombocytosis or palpable splenomegaly. The two-year postoperative hematologic remission may be attributed to any or all of the following: (1) P^{32} administration (4 millicuries in June, 1955); (2) blood loss, both therapeutic and postoperative; (3) the natural course of the disease; and (4) removal of the renal cancer. The longer the duration of the hematologic normality, the less likely become the first three causes. There is no evidence so far for myelofibrosis, myelosclerosis or leukemia.

CASE IX. A. G. (No. 109104), a fifty-eight year old Russian-born Jewish housewife, was admitted on September 15, 1952, for investigation of recent paroxysmal pains and paresthesias involving the entire left half of her body. She had a history of documented hypertension for at least fifteen years, without complication; she also had asymptomatic gallstones, and had occasionally passed small urinary calculi. Physical examination was normal except for a blood pressure of 260/140 mm. Hg and cardiac enlargement to percussion. The hemoglobin was 20.5 gm. per cent; red blood cells, 6.22 million per cu. mm.; and white blood cells, 10,500 per cu. mm., with a normal differential count; hematocrit, 65.3 per cent; platelets, 134,000 per cu. mm. The urine showed 1 plus proteinuria and occasional red and white blood cells. Examination of the bone marrow revealed normoblastic hyperplasia. An electrocardiogram showed changes suggesting left ventricular hypertrophy. The uric acid was 7.5 mg. per cent; the non-protein nitrogen was 44 mg. per cent. A chest film confirmed a moderate degree of cardiac enlargement, and the lung fields were clear.

As part of the investigation of the patient's hypertension, an intravenous pyelogram was performed which revealed a large mass attached to the lower pole of the left kidney; definite distortion of the left lower calyces was also noted. The radiological diagnosis of left renal tumor was made, and recent review of the films confirms this diagnosis.

The patient's neurological symptoms were ascribed to cerebral spasm. Therapy for her polycythemia consisted of removal of 750 cc. blood via two phlebotomies. Further diagnostic work-up of her presumptive left renal tumor was scheduled but the patient left the hospital before this could be accomplished, and has subsequently remained lost to attempts at follow-up.

Comment: This patient's polycythemia and renal tumor were both discovered incidentally during the course of a hospital admission for hypertensive disease; both conditions were apparently asymptomatic at the time of discovery. The polycythemia was not accompanied by leukocytosis, thrombocytosis or palpable splenomegaly. The mass in the kidney seen on intravenous pyelography was never confirmed by histologic examination, but its radiologic appearance was considered typical of renal carcinoma. There was no apparent cause for a secondary polycythemia, other than this renal mass.

CASE X. J. M., a sixty-nine year old retired white policeman and Army captain, American-born of Jewish descent, was first admitted to the U. S. Naval Hospital, St. Albans, New York, on July 2, 1956, for treatment of polycythemia. He had always been well except for easy fatiguability for several years, for which he had consulted a private physician in May, 1954. The physical examination had been within normal limits. In October, 1955, he had complained of nausea, epigastric pains, and exertional dyspnea and angina. He was then found to have a cyanotic face; epigastric tenderness; hemoglobin, 17 gm. per cent; red blood cells, 5 to 7 million per cu. mm.; and urine, negative for albumin, glucose and sediment. X-ray films showed normal heart and lungs, and gastric ulceration, apparently benign, on the lesser curvature, with antral gastritis. By March, 1956, this had responded radiographically and clinically to medical treatment. In May, his hemoglobin was

16.5 gm. per cent, and an electrocardiogram was normal.

However, dyspnea and angina continued, as did weight loss from 152 to 132 pounds in six months. In June, 1956, cyanosis had increased; hemoglobin was 17.0 gm. per cent; red blood cells, 8.8 million per cu. mm.; and white blood cells, 7,000 per cu. mm., with a normal differential count; the hematocrit was 59 per cent; platelets were slightly increased on smear; and reticulocytes were 1.3 per cent. The urine was normal except for many red blood cells in the sediment. The blood urea nitrogen was 8 mg.; uric acid, 5.2 mg.; albumin, 4.5 gm.; and globulin, 2.8 gm. per cent. He was hospitalized elsewhere, with findings of hemoglobin, 16.9 per cent; red blood cells, 5.6 million per cu. mm.; and white blood cells, 5,750 per cu. mm.; hematocrit, 63 per cent; blood urea nitrogen, 20 mg.; and uric acid, 3.6 mg. per cent. Urinalysis was completely negative. Phlebotomy was performed on June 14 and 15, with removal of 500 cc. of blood each time. He then entered the St. Albans Naval Hospital for further study and treatment.

Physical examination was within normal limits, except for a plethoric face, cyanotic lips, and a moderately enlarged prostate gland. The blood pressure was 120/70 mm. Hg. Neither liver nor spleen was palpable. No abnormalities were found on urinalysis, chest films, electrocardiogram, or a complete battery of pulmonary function tests. A gastrointestinal series showed old gastric and duodenal scars, without active craters. Before phlebotomy, hemoglobin varied on repeated determinations between 15 and 17.5 gm. per cent, red blood cells between 6.5 and 8.3 million per cu. mm., white cells between 5,450 and 6,800 per cu. mm., and hematocrit from 57 to 61 per cent. A single platelet count was 493,000 per cu. mm. and a reticulocyte count 0.6 per cent. The prothrombin time was 14 seconds (normal, 13 seconds). The serum uric acid was 3.6 mg. per cent. The arterial oxygen saturation was 92.4 per cent with the patient at rest, 91.8 per cent with the patient exercising. Bone marrow aspiration showed erythroid hyperplasia.

Treatment consisted of an ulcer regimen and three phlebotomies with the removal of 500 cc. of blood each, on July 30, August 11, and August 20. On August 6, I^{131}-tagged albumin studies showed a total blood volume of 8,402 cc., or 139 cc./kg. (normal, 78 ± 9) [*27*]; plasma volume, 3,865 cc., or 64 cc./kg. (normal, 44 ± 6); red blood cell volume, 4,537 cc. or 75 cc./kg. (normal, 34); and hematocrit, 54 per cent. On August 30, a week after discharge, his hemoglobin was 13 gm. per cent; red blood cells, 5.3 million per cu. mm.; white blood cells, 6,850 per cu. mm.; and platelets, 259,000 per cu. mm.

On September 9, 1956, he was readmitted because of sudden suprapubic pains and gross hematuria of one day's duration. The physical examination was as before, although his weight had fallen to 125 pounds. The hemoglobin was 13 gm. per cent; red blood cells, 7.8 million; white blood cells, 6,200 per cu. mm.; and hematocrit, 56 per cent. The next day, blood studies with Cr^{51} disclosed a total blood volume of 4,900 cc. or 86 cc./kg. (normal, 70 ± 5); plasma volume, 2,250 cc., or 40 cc./kg. (normal, 40 ± 5) [*28*]; and red blood cell volume, 2,650 cc., or 46 cc./kg. (normal, 30 ± 0.5) [*29*].

At first, the hematuria was thought to result from polycythemia with renal infarction, and on September 20, phlebotomy was performed with removal of 1,000 cc. of blood. The serum uric acid was 5.0 mg. per cent on September 26. On October 2, 2.94 millicuries of P^{32} were injected intravenously. Persistent hematuria led to urological investigation, resulting in a left nephrectomy for tumor performed on November 28. The tumor proved to be clear cell carcinoma with regional lymph node involvement. At operation, the subcutaneous and deeper vessels appeared engorged, and blood loss was estimated at 3,100 cc., of which 2,500 cc. were replaced by transfusion. Skeletal and chest roentgenograms showed no metastases, and the patient was discharged on December 17.

Since discharge the patient had remained asymptomatic. Serial blood counts and blood volume determinations have been within normal limits. On September 9, 1957, I^{131}-tagged albumin studies showed a total blood volume of 5,025 cc. or 74 cc./kg.; plasma volume, 3,025 cc., or 44 cc./kg.; red blood cell volume, 2,000 cc., or 30 cc./kg.; and hematocrit, 39.7 per cent.

Comment: Polycythemia, preceding renal carcinoma symptomatically by several months, was characterized by normal leukocyte and platelet counts, normal levels of serum uric acid, and a normal-sized spleen. Pulmonary function and arterial oxygen saturation were likewise normal, ruling out anoxia as a stimulus to erythropoiesis. Multiple phlebotomies, operative blood loss, and P^{32} administration make it impossible to determine the hematological response to nephrectomy alone.

COMMENTS

Incidence. As already noted, our nine cases from the Presbyterian Hospital constituted 4.4 per cent of 205 patients in whom polycythemia could be attributed to no known cause, such as cardiopulmonary or endocrine disorder or exposure to chemical agents. Excluding these nine cases from the category of polycythemia vera, for reasons to be discussed, the ratio of polycythemia associated with renal carcinoma to polycythemia vera becomes 9:197, or 4.6 per cent. This figure does not differ greatly from Videbaek's [*14*] 2:123 (1.6 per cent) or Lawrence's [*8*] 2:157 (1.3 per cent). Our nine pa-

tients with coexisting polycythemia comprised 2.6 per cent of some 350 cases of carcinoma of the renal parenchyma which were seen at the Presbyterian Hospital between 1929 and 1957. This percentage resembles the 1.8 per cent reported by Berger and Sinkoff [*12*] among 273 cases of hypernephroma.

Host Factors. Table I summarizes data from twelve previously reported cases and ten of our own.

Age and sex incidence follow the distribution of patients with either polycythemia vera or renal carcinoma, both of which occur in middle or late adult life and chiefly in males. The average age of the twenty-two patients in Table I was 58.1 ± standard error 1.5 years when first seen. Among 197 patients with primary polycythemia in the Presbyterian Hospital, the average age of onset was 53.6 ± 0.9 years [*15*], and similar values were obtained in two large series of patients with renal carcinoma [*12,16*]. Of the twenty patients in whom the time of onset for both conditions could be compared, it coincided within a year in seventeen. Tumor preceded polycythemia by some four years in our Case VIII, and vice versa in our Case I, and in Videbaek's [*6*] Case II. Both of the last mentioned patients are further distinguished from the others by the presence of splenomegaly, leukocytosis and thrombocytosis.

The predominance of males (17:5) occurs likewise in polycythemia vera [*15*] (2:1) and renal carcinoma (65:35) [*12*].

The racial or ethnic distribution presumably reflects the interest of Scandinavian authors in the syndrome and the increased incidence of polycythemia among Jews [*15*]. It is, however, barely possible that the apparent Scandinavian predilection has a genetic basis. Our nine patients from the Presbyterian Hospital included a Norwegian, a Swede and a Latvian,* whereas only 4 per cent of 197 patients with polycythemia vera from the same hospital were Scandinavians. While the difference is probably statistically significant ($p < .04$), confirmation on much larger numbers is needed before any practical conclusions can be drawn.

The ABO blood group distribution of six of our patients was unremarkable; one had type A, two type B, and three type O.

As with renal carcinomas generally [*16*], the tumors occurred with equal frequency on either side; ten were in the right kidney, ten in the left, and two bilateral.

Nature of the Renal Carcinoma. The gross and microscopic pathologic conditions in Cases I, III, V, VI, VIII and X, were reviewed. In Case I, the specimen weighed 330 gm. and the sections revealed a papillary adenocarcinoma of the kidney. This tumor and its surrounding renal parenchyma showed no histological difference from the picture presented by similar malignancies in patients who did not have associated polycythemia. In Cases III, V, VIII and X, the specimens weighed 522, 434, 524 and 825 gm., respectively. The weight was not stated in Case VI. The microscopic picture in all these cases was "clear cell carcinoma." In Case V, however, there was a granular cell component in addition; all showed marked vascularity, hemorrhage and fibrosis. Comparison, however, with ten carcinomas of the kidney selected at random from our renal tumor series (obtained from patients *without* polycythemia) showed no histologic difference between the two groups. Microscopic study of the surrounding renal parenchyma in both series revealed no definite extramedullary hemopoietic foci.

It is our opinion, based on the study of sections processed in the routine laboratory technic and staining, that there is no significant histologic finding in cancer of the kidney and of the adjacent parenchyma which is unique to patients with polycythemia.

Nature of the Polycythemia. Table I shows that most patients with coexisting polycythemia and renal carcinoma lack splenomegaly, leukocytosis and thrombocytosis. Prominent exceptions are the two patients already mentioned (Videbaek's Case II and our Case I), in whom polycythemia apparently antedated the tumor by several years and who may well have had polycythemia vera; and two additional patients, those of Fairley and Medvei. Thus the polycythemia in the present syndrome is more properly an erythrocytosis. Splenomegaly and pancythemia are usually, although not always, present in polycythemia vera, but typically absent in the idiopathic polycythemia of childhood [*15,17,18*] and in polycythemia secondary to arterial oxygen unsaturation, chemical poisoning, endocrine disorders, subtentorial tumor (especially cerebellar hemangioblastoma) [*19*] and uterine myoma [*15*].

* Latvia was colonized early by Danes and was a Swedish province from 1621 to 1721.

Arterial oxygen saturation determinations were normal in the four patients tested, and bone marrow examinations showed only increased erythropoiesis in thirteen patients so studied. Elevated blood volumes were found in the three patients in whom the determination was performed (our Cases I, V and X); in each case, the increase in blood volume was attributable to a striking elevation in the red cell volume. These findings are consistent with those of Gibson et al. [*31*] in polycythemia vera, and with those of Berlin et al. [*32*] for secondary polycythemia.

A significant feature of the polycythemia associated with renal carcinoma is its occasional remission following nephrectomy. Table II summarizes the pertinent data. Forssell [*5*] and Gros [*9*] have each reported one patient in whom hematologic remission for fourteen months and three years, respectively, could be reasonably ascribed to the nephrectomy. (In Videbaek's [*6*] case, which is often quoted, the patient had received P^{32} therapy prior to nephrectomy, and, at the time when the case report appeared, had been followed up for only six months after operation). Forssell's patient is further noteworthy in that his polycythemia recurred fourteen months postoperatively, at which time a "hypernephroma" was discovered in the remaining kidney. Of our five patients who underwent nephrectomy, the patient in Case III has had a complete hematologic remission for eleven years to date, without other specific therapy. In Case VIII, the patient has had normal blood values for two years, and it is unlikely that the single dose of 4.0 millicuries of P^{32} administered twenty-eight months ago, or his preoperative and operative blood loss (much of which was replaced by transfusion) can account for his long remission. With the passage of time, nephrectomy appears to be the most likely cause. In Case VI there was a complete hematologic remission for sixteen months following nephrectomy (although here, too, massive blood loss at operation may have contributed to the remission); uremia and anemia then developed, and the patient died twenty-eight months after operation. In Case X the patient was operated upon in November, 1956, and was well ten months after operation, but he had received 2.94 millicuries of P^{32}; like Videbaek's patient, he had had other therapy and too short a follow-up period to assess the effect of tumor removal alone. Finally, in Case V death occurred as a result of uremia and metastatic malignancy four months after operation. The patient became anemic shortly before death. Therefore this case, too, cannot be used to assess the effect of nephrectomy.

Thus four unequivocal and four possible cases of disappearance of polycythemia following removal of an associated renal carcinoma have now been reported. Stated otherwise, all eight patients with both polycythemia and renal carcinoma who underwent nephrectomy had hematologic remissions (although, in four of the cases, other factors admittedly may have played a part). The conclusion seems clear, as Forssell [*4*] first pointed out in 1946, that polycythemia in the syndrome under discussion is, in some cases at least, secondary to renal carcinoma.

Regression of polycythemia following removal of the tumor has likewise been noted in five patients with uterine myoma [*15*]; in several with cerebellar hemangioblastoma [*19*]; and in one with benign renal adenoma [*13*]. These neoplasms must likewise be capable, at rare times or in rare patients, of evoking erythropoiesis.

Possible mechanisms: The mechanisms whereby renal neoplastic disease can cause polycythemia are admittedly speculative at this time. Following the similar discussion of Ward, Foltz and Knopp [*19*] for cerebellar hemangioblastoma, the following possibilities can be listed:

(1) *Erythropoiesis may occur in the tumor or in surrounding renal parenchyma.* Although the kidney and the renal pelvis are occasional sites of extramedullary erythropoiesis, particularly in children, sections of tumor and of surrounding normal tissue in our patients with the syndrome under discussion showed no significant erythroblastic foci.

(2) *The polycythemia may be secondary to arterial oxygen unsaturation;* this being the result of either (a) arteriovenous shunts in the tumor, (b) pulmonary metastases, or (c) impaired diaphragmatic excursion, due to mechanical interference by the tumor. Not only has the oxygen saturation been normal in the few patients tested, but no shunts have been found in the tumors in our series, pulmonary metastases have not been reported to cause arterial unsaturation, and the renal tumor has not hampered respiration in any of the patients under discussion.

(3) *Production of an erythropoietic substance may occur in the tumor or in the adjacent renal parenchyma.* A large body of experimental data has been gathered in recent years supporting the concept

TABLE I

PATIENTS WITH POLYCYTHEMIA AND RENAL CARCINOMA

No.	Source	Age (yr.) and Sex	National Origin	Blood Values*					Bone Marrow Examination	Palpable Spleen	Arterial Oxygen Saturation (%)	Hematuria	Pyelographic Findings	Presence of Flank Mass	Nephrectomy	Autopsy Findings
				Hemoglobin	Hematocrit (%)	Red Blood Cells (M/cu. mm.)	White Blood Cells (cu. mm.)	Platelets (cu. mm.)								
1	Medvei [2], 1934	62,M	Austria	140%	....	8.0	11,600	.....	Increased erythropoiesis	Yes	.....	None	.....	No	No	Right hypernephroma metastatic to lung, liver, elbow joint and retroperitoneal nodes
2	Fairley [3], 1945	48,M	Russia (Jewish)	20.4 gm.	....	8.4	8,250	Normal	.....	Yes	.....	Microscopic	Tumor, right	No	Yes	Not performed
3A	Forssell [4], 1946	49,M	Finland	121%	....	8.32	Normal	673,000	Increased erythropoiesis	Yes	.....	Gross	.....	No	Yes (right)	.....
3B	Forssell [5], 1947	50	.....	114%	58	7.28	Normal	.....	Increased erythropoiesis	Yes	.....	Gross	Tumor, left	No	No	Left hypernephroma, metastatic to right adrenal gland
4	Forssell [5], 1954	71,F	Finland	128%	61	8.15	6,800	185,000	Increased erythropoiesis	No	.....	Abundant red blood cells in sediment	Tumor, right	No	No	Not performed
5	Forssell [5], 1954	66,M	Finland	109%	....	6.00	5,900	Normal	.....	No	.....	120/hpf	.....	No	No	Left hypernephroma, metastatic to lungs and adrenals
6	Forssell [5], 1954	65,M	Finland	120%	....	6.18	3,000	Normal	.....	No	.....	Gross	.....	Yes	No	Right hypernephroma
7	Videbaek [6], 1950	55,M	Denmark	147%	....	8.67	7,600	302,000	.....	No	.....	Gross	.....	No	No	Left hypernephroma metastatic to lung
8	Videbaek [6], 1950	57,F	Denmark	95%	....	6.90	70,000	760,000	Increased erythropoiesis, marked	Yes	.....	Microscopic	.....	No	No	Left hypernephroma metastatic to liver
9	Videbaek [6], 1950	45,F	Denmark	130%	55	10.65	5,080	100,000	Increased erythropoiesis	No	.....	Microscopic	Tumor, right	No	Yes	Patient alive
10	Gros [9], 1955	53,M	Germany	125%	....	7.5	6,300	160,000	.....	No	.....	Gross	Tumor, left	Yes	Yes	Patient alive
11	Moe [10], 1956	55,M	Norway	140%	....	7.2	6,600	514,000	Increased erythropoiesis	No	.....	None	.....	No	No	Right hypernephroma metastatic to pleura and brain

TABLE I (*Continued*)

PATIENTS WITH POLYCYTHEMIA AND RENAL CARCINOMA

No.	Source	Age (yr.) and Sex	National Origin	Blood Values*					Bone Marrow Examination	Palpable Spleen	Arterial Oxygen Saturation (%)	Hematuria	Pyelographic Findings	Presence of Flank Mass	Nephrectomy	Autopsy Findings
				Hemoglobin	Hematocrit (%)	Red Blood Cells (M/cu. mm.)	White Blood Cells (cu. mm.)	Platelets (cu. mm.)								
12	Herbeuval [*11*], 1957	48,M	France	165%	....	8.4	8,500	250,000	Increased erythropoiesis	?	.....	None	Negative	No	No	Right hypernephroma metastatic to lungs; gastric ulcer
13	Present report Case I	49,M	Russia (Jewish)	22.4 gm.	....	9.7	15,000	437,000	.....	Yes	.....	Gross	.....	Yes	No	Right renal adenocarcinoma metastisising to left kidney; miliary tuberculosis; right pyelonephritis; gout
14	Present report Case II	40,M	Italy	22.5 gm.	....	8.0	7,200	198,000	.....	No	90 (at rest)	Rare/hpf	Tumor, right	No	No	Not performed
15	Present report Case III	59,M	Sweden	20.0 gm.	....	8.2	9,050	202,000	.....	No	92 (at rest)	Occasional/hpf	Tumor, right	Yes	Yes	Patient alive
16	Present report Case IV	54,M	Poland (Jewish)	125%	67	7.4	7,000	280,000	Compatible with polycythemia vera	No	.....	Rare/hpf	Tumor, left	Yes	No	Not performed
17	Present report Case V	67,F	Russia (Jewish)	19.0 gm.	66.1	7.2	9,700	192,000	.....	No	.....	Gross	Tumor, left	Yes	Yes	Not performed
18	Present report Case VI	72,M	Poland (Jewish)	18.0 gm.	60	6.2	15,300	370,000	Increased erythropoiesis	Transient	.....	6 to 12/hpf	Tumor, left	No	Yes	Not performed
19	Present report Case VII	70,M	Norway	18.7 gm.	....	6.3	5,700	.....	.....	No	.....	Gross	Tumor, right	Yes	No	Not performed
20	Present report Case VIII	59,M	Latvia	23.2 gm.	73.2	9.0	8,200	140,000	Increased erythropoiesis	No	98.4 (at rest); 97.1 (after exercise)	Rare/hpf	Tumor, left	Yes	Yes	Patient alive
21	Present report Case IX	58,F	Russia (Jewish)	20.5 gm.	65.3	6.22	10,550	134,000	Increased erythropoiesis	No	.....	Occasional/hpf	Tumor, left	No	No	Patient lost to follow-up
22	Present report Case X	69,M	U.S.A. (Jewish)	17.5 gm.	63.0	8.8	7,000	493,000	Increased erythropoiesis	No	92.4 (at rest); 91.8 (after exercise)	Gross	Tumor, left	No	Yes	Patient alive

* All blood values are the highest obtained for each patient.

TABLE II

PATIENTS WITH POLYCYTHEMIA AND RENAL CARCINOMA WHO UNDERWENT NEPHRECTOMY

No.	Source	Degree of Hematologic Remission after Nephrectomy	Duration of Remission	Other Possible Contributing Factors to Remission of Polycythemia
1	Forssell [*4,5*]	Complete	14 mo.; following right nephrectomy; patient again became polycythemic when hypernephroma developed in left kidney	No specific therapy for polycythemia
2	Videbaek [*6*]	Complete	6 mo.; patient still alive when reported in 1950	Radioactive phosphorus (6.0 mc.) therapy; phlebotomy preoperatively.
3	Gros [*9*]	Complete	3 yr.; patient still alive when reported in 1955	No specific therapy
4	Present report Case III	Complete	11 yr.; patient still alive in September, 1957	No specific therapy
5	Present report Case V	Complete; anemia prior to death	4 mo.; patient then died of uremia and metastatic hypernephroma	Phlebotomy (400 cc.) preoperatively; uremia; metastatic neoplasia
6	Present report Case VI	Complete; anemia prior to death	2 yr., 4 mo.; patient then died of uremia	Massive blood loss associated with nephrectomy
7	Present report Case VIII	Complete	2 yr.; patient still alive in September, 1957	Radioactive phosphorus (4.0 mc.), June, 1955; phlebotomy (2,000 cc.) preoperatively; massive blood loss 2 weeks post-nephrectomy, associated with prostatectomy
8	Present report Case X	Complete	10 mo.; patient still alive in September, 1957	Radioactive phosphorus (2.94 mc.), October, 1956; phlebotomy (2,000 cc.) preoperatively; massive blood loss associated with nephrectomy
9	Fairley [*3*]	Blood values normal 2 yr. prior to nephrectomy; no change following nephrectomy	.....	Phenylhydrazine therapy; phlebotomy, repeated; induced remission 2 yr. prior to nephrectomy

of humoral regulation of erythropoiesis. A plasma erythropoietic factor has been demonstrated in patients with polycythemia vera [*33,34*], secondary polycythemia [*34*], and in the concentrated serums of normal subjects [*35*]. The source of this humoral factor, usually designated as "erythropoietin," is not known. However, Jacobson and co-workers [*26*] have recently reported evidence suggesting that erythropoietin is produced in the kidneys. It may therefore be postulated that, in a certain small percentage of renal neoplasms, abnormally large quantities of erythropoietin are synthesized by either the tumor or the surrounding renal parenchyma. Liberation of erythropoietin into the systemic circulation results in erythrocytosis, presumably due to a direct action by the hormonal factor on the bone marrow.

Ancillary evidence supporting this hypothesis may be cited. Renal tumors (as well as neoplasms arising from the bronchus, uterus and ovary) have been reported in association with metabolic abnormalities simulating hyperparathyroidism, with regression of these changes following excision of the tumor [*20,21*]. Production of a parathyroid hormone-like substance by these tumors has been postulated. In addition, renal disorders other than carcinoma have been associated with polycythemia, for example, benign adenoma [*13*], polycystic disease [*25*], and unilateral tuberculosis in a patient with a congenitally absent kidney [*15*].

On the other hand, cerebellar hemangioblastoma and uterine fibroma have also been reported in association with polycythemia, as have gastric carcinoma metastatic to liver [*22*], primary hepatoma [*23*] and prostatic carcinoma [*24*]. Increased renal production of erythropoietin, as postulated to explain the polycythemia occurring with renal carcinoma, could not be invoked as a possible mechanism explaining the polycythemia observed in these widely varied neoplastic processes. In addition, it appears unlikely that all these organs have the potential ability to produce an erythropoietic substance following malignant degeneration.

Practical considerations: Whatever the mechanism, the fact remains that an appreciable percentage of patients with polycythemia, some 4 per cent in our experience, have renal clear cell carcinoma. The importance of careful abdominal palpation for a mass in the flank is obvious. Abdominal radiography (a single flat film) to demonstrate renal outlines may be reasonably recommended in addition. There can be no doubt of the necessity for urologic investigation of hematuria in polycythemia. Hematuria, gross or microscopic (i.e., "occasional" to "many" red blood cells per high power field), occurred in twenty patients with polycythemia vera among 183 in whom urine was analyzed [*15*]. Excluding five patients with chronic prostatitis or nephritis, fifteen or 8.2 per cent remain. Videbaek's [*14*] series includes nine patients of 123 with hematuria, or 7.3 per cent. In contrast, nineteen of the twenty-two documented cases of polycythemia with renal carcinoma, or 86 per cent, demonstrated hematuria. Thus, if 4 per cent of patients with polycythemia have renal carcinoma, and if almost all exhibit hematuria, the chances are about one in three (4:4 plus 8) that any given patient with polycythemia and hematuria has an associated renal tumor. The assumption that hematuria is a benign manifestation of the polycythemic process can lead to serious error.

SUMMARY

Ten patients with polycythemia and renal carcinoma are presented and twelve previously documented cases from the literature summarized. The syndrome occurred in some 4.4 per cent of 205 patients with polycythemia and 2.6 per cent of 350 patients with renal carcinoma seen in the Presbyterian Hospital.

The renal tumors, as well as adjacent parenchymal tissues, were not histologically unique in the six specimens studied.

The polycythemia was, for the most part, a simple erythrocytosis without marked splenomegaly, leukocytosis or thrombocytosis. It thus resembled "secondary" rather than primary polycythemia except that it was not dependent upon arterial oxygen unsaturation. Two of our patients had complete hematologic remission following nephrectomy, one for two years and the other for eleven years. Two others from the literature had similar remissions for fourteen months and three years. Of the twenty-two patients thus far described, all eight who underwent nephrectomy had subsequent hematologic remission, whether or not other factors may have played a part. The polycythemia can therefore be regarded as secondary to the renal tumor, as maintained by previous authors. A similar erythropoietic effect has been described for uterine myoma and cerebellar hemangioblastoma, as well as benign renal adenoma and several varieties of carcinoma.

The mechanism for the erythrocytosis is unknown, but probably an erythropoietic substance is produced, perhaps in the tumor or in the neighboring renal parenchyma.

Whatever the mechanism and its site of action, the appreciable coincidence of polycythemia and renal carcinoma makes mandatory the urologic investigation of hematuria in polycythemia.

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ADDENDUM

Since completion of this manuscript, several additional cases of polycythemia associated with renal carcinoma have appeared in the literature [*36–39*]. Also, Dr. A. Videbaek has advised us that his patient (Table I, Case IX) is still alive, nine years post-nephrectomy, and in complete remission from her polycythemia. Dr. H. Gros informs us that his patient (Table I, Case X) died in 1956 of a rectal neoplasm, and had suffered no recurrence of his polycythemia prior to death.

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Non-Addisonian Megaloblastic Anemia*

The Intermediate Megaloblast in the Differential Diagnosis of Pernicious and Related Anemias

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THE differentiation of classic Addisonian pernicious anemia from other types of megaloblastic anemia may be difficult. Megaloblastic bone marrow has been noted in well documented instances of tropical and non-tropical sprue [*1–13,151,152*], nutritional macrocytic anemia [*14–30,151,152*], megaloblastic anemia of pregnancy [*31–47,151*], megaloblastic anemia of infancy [*48–56*], various intestinal disorders characterized by blind loops, fistulas, or massive diverticulosis [*57–79,151,152*], corrosive [*80*] and neoplastic [*81–85*] lesions of the stomach, chronic liver disease [*86,87*], and carcinomatosis of the bone marrow [*88,89*]. Megaloblastic anemia has also developed following total or subtotal gastric resection [*90–106,151,152*], after the administration of anticonvulsant drugs [*107–118,151*], and as a result of vitamin C deficiency [*119*] and of parasitic infestation [*120–126*]. Until the recent availability of radiocobalt-labelled cyanocobalamin for measurement of absorption and utilization of vitamin B_{12} [*127–129*], the differentiation of pernicious anemia from the other megaloblastic anemias depended largely on the presence or absence of the typical clinical picture: megaloblastic erythropoiesis, histamine-fast achlorhydria, and signs of posterolateral sclerosis. However, histamine-fast achlorhydria may be found in megaloblastic anemias other than pernicious anemia, although in the non-Addisonian varieties free acid often returns following successful therapy [*9,13,16,22,41,44,71,73, 121,123*]. Thus histamine-fast achlorhydria was noted in sixteen of thirty-one cases of non-tropical sprue by Cooke et al. [*9*], and other observers have reported an even greater incidence [*2,6,13*]. It was also present in thirty-one of 148 acceptable cases of megaloblastic anemia of pregnancy in which this parameter was measured [*34,37,39,41–44,47*], and in eleven of fifteen cases of megaloblastic anemia of infancy [*50*]. Similarly, achlorhydria was present in a significant percentage of cases of nutritional macrocytic (megaloblastic) anemia [*21,30*], Diphyllobothrium latum infestation [*121–124*], and megaloblastic anemia associated with various gastrointestinal disorders [*60,61,67,74,75,79,81–85,90,97, 98,103,151*]. Neurologic signs suggestive of posterolateral sclerosis have also been described in a variety of non-Addisonian megaloblastic anemias [*60,62,73,82,84,85,91,97,98,120,125*] and cannot therefore be considered as diagnostic of pernicious anemia.

In many cases of megaloblastic macrocytic anemia, certain abnormalities in the peripheral blood and the bone marrow suggest the non-Addisonian nature of the anemia. These deviations of erythropoiesis from the frankly megaloblastic type found in pernicious anemia are helpful in elucidating the true nature of the macrocytosis.

In pernicious and related anemias, the primitive red cell matures (megaloblastic erythropoiesis) in a manner morphologically and physiologically different from the development of the red cell in the normal and in all other anemias (normoblastic erythropoiesis). It was previously believed that the earliest recognizable red cell precursor was common to both normoblastic and megaloblastic lines of development, but more recently most investigators have been able to differentiate morphologically between that progenitor giving rise to normoblasts ("pronormoblast") and that found in megaloblastic erythropoiesis ("promegaloblast") [*130*]. The promegaloblast differs from the pronormo-

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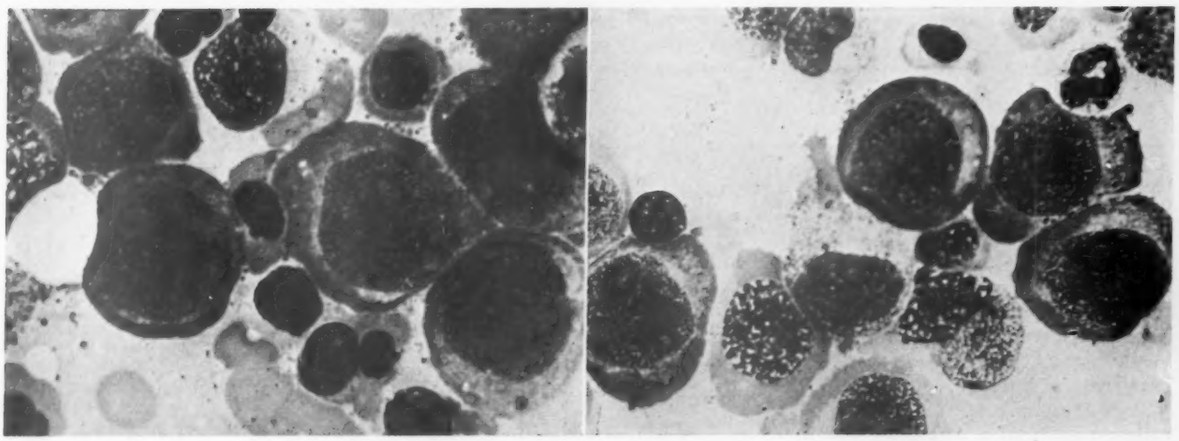

1 2

FIGS. 1 and 2. True megaloblastic [*1*] and modified (intermediate) [*2*] megaloblastic erythropoiesis at comparable early developmental stages. The pernicious anemia promegaloblasts [*1*] display relatively greater cytoplasmic/nuclear ratio and a more reticular network than do the modified or intermediate promegaloblasts of non-Addisonian megaloblastic anemia [*2*]. Unfortunately the lack of nuclear-cytoplasmic asynchromism in the modified forms is evident only in color photographs. Both patients had comparable hemoglobin values (2.6 to 2.9 gm. per cent).

blast in that the nuclear chromatin has a finer, more homogenous, lacy structure, and is more evenly distributed, without any tendency toward clumping. The promegaloblast is larger than its pronormoblast counterpart, there is a larger amount of cytoplasm in proportion to the size of the nucleus, and the nucleoli are more difficult to discern through the fine mesh-like chromatin. As these precursor cells mature into basophilic, polychromatophilic and orthochromatic megaloblasts and normoblasts, respectively, the delicate unclumped nature of the nuclear chromatin persists in the megaloblastic series, but is rapidly lost and superseded by coarse clumped nuclear chromatin in the normoblastic series. The cytoplasm in the megaloblastic series is in general more eosinophilic (i.e., hemoglobin appears earlier) than is the cytoplasm in the normoblastic series at comparable stages of development. This disparity between maturity of cytoplasm and of nucleus ("nuclear-cytoplasmic asynchronism" [*131*]) is a striking characteristic of the megaloblasts of pernicious anemia.

These well recognized morphologic features distinguish the two extremes of erythropoiesis, i.e., megaloblastic (as found in pernicious anemia), and normoblastic (as found normally and in hemolytic and hemorrhagic anemias). However, certain non-Addisonian megaloblastic anemias are characterized by lines of red cell development "morphologically intermediate between unequivocal megaloblastic erythropoiesis and normoblastic erythropoiesis," i.e., by "intermediate megaloblasts" [*131,133*]. The slight but definite morphologic deviations which distinguish "intermediate" (modified) megaloblasts from unequivocal, "full-blown" megaloblasts at comparable stages of development have been especially emphasized in the British literature [*8,19,20,132–134*]. The intermediate forms in their early developmental stages, display the abnormal mitoses, irregular chromatolysis and pronounced karyorrhexis also found in the megaloblastic erythropoiesis of pernicious anemia. However, the "asynchronism" between the maturity of the nucleus and that of the cytoplasm which is so characteristic of pernicious anemia is strikingly lacking in these intermediate forms [*19,20,24,26*]: the megaloblasts of pernicious anemia display a more reticular (primitive) chromatin network (Fig. 1), yet a more mature (eosinophilic) cytoplasm than do the corresponding stages of intermediate megaloblasts. The intermediate megaloblasts (Fig. 2) also appear more compact and thicker than the corresponding developmental stages of the megaloblasts of pernicious anemia.

It is the purpose of this report to emphasize these slight aberrations and to point out their usefulness in differentiating uncomplicated pernicious anemia from non-Addisonian megaloblastic anemias. Four patients are presented in whom the bone marrow showed modified megaloblastic erythropoiesis; this was the first clue to the ultimate diagnosis of non-pernicious megalo-

TABLE I
ADMISSION LABORATORY DATA

Data	Case I	Case II	Case III	Case IV
Hemoglobin (gm. per cent)	8.5	2.65	5.8	8.3
Red blood cells (10^6/cu. mm.)	2.31	0.92	2.92	2.46
Packed red cell volume (ml./100 ml.)	27.5	9.0	29.0	21.5
Reticulocytes (%)	2.4	0.6	2.1	5.6
Mean corpuscular volume (cubic microns.)	120.	98.	100.	88.
Mean corpuscular hemoglobin ($\mu\mu$g.)	32.5	28.4	20.	33.
Mean corpuscular hemoglobin content (%)	31.5	29.4	20.	37.
White blood cells (cu. mm.)	4,400	3,100	7,500	4,500
Platelets (cu. mm.)	166,000	72,000	134,000	174,000
Macrocytosis	++	+++	+	+
Anisocytosis	+++	++	+	++++
Poikilocytosis	+	+	0	++++
Microcytosis	+	++	++	+
Hypersegmented polymorphonuclear cells	+	++	+	+
Bilirubin, direct (mg. per cent)	0.3	0.1	0.3	0.3
Total (mg. per cent)	0.45	1.5	2.1	2.0
Serum iron (μg./100 ml.)	45.	58.	48.	120.
Total iron binding capacity (μg./100 ml.)	258.	250.	315.	403.
Stool guaiac reaction	Negative	++	+++	Negative
Free acid (histamine stimulation)	Absent	Present	Absent	Present

blastic anemia in each instance. The nature of these aberrations, their possible pathogenesis, their significance and recognition are discussed.

CASE REPORTS

CASE I. A. T., a sixty-two year old white housewife, was admitted to The Mount Sinai Hospital in January 1955 because of disorientation and incoherence for one month. For one year before admission she had complained of slight weakness in both legs and occasional episodes of diarrhea. In 1948 exploratory laparotomy had been performed at another hospital because of rapid swelling of the abdomen; an 11-pound pancreatic cyst was removed, but details of the operation were not available. Mild diabetes developed but was easily controlled with protamine zinc insulin. There was no history of other illness or medication, and no history of blood loss or exposure to toxic agents. The remainder of the past history and the family history were irrelevant.

Physical examination revealed an elderly white lady with gray hair, normal-sized earlobes, and moderate pallor without icterus. The tongue was smooth but not red. The liver edge was palpable at the right costal margin. A firm lobulated mass, the size of a grapefruit, was present in the right lower quadrant of the abdomen. Neurologic examination revealed depressed knee and ankle reflexes, and normal plantar responses. Vibratory sensation was diminished bilaterally below the iliac crest. The rest of the examination revealed no abnormalities.

Initial laboratory studies (Table I) revealed macrocytic anemia and leukopenia with hypersegmented polymorphonuclear leukocytes. The blood smear showed marked anisocytosis, minimal poikilocytosis, and many hypochromic red cells. Bone marrow aspiration showed a hypercellular preparation in which the red cell precursors were morphologically intermediate between megaloblastic and normoblastic cells. Many giant metamyelocytes were present. Histamine-fast achlorhydria was demonstrated on three occasions. Serum iron was 45 μg./100 ml. The vitamin A tolerance test suggested impaired intestinal absorption, and an oral glucose tolerance test showed a diabetic curve. The serum vitamin B_{12} (Euglena method) was 20 $\mu\mu$g./ml.

A Schilling test [*128*] demonstrated impaired intestinal absorption of $Co^{60}B_{12}$. This impaired absorption was not corrected by simultaneous administration of intrinsic factor.

X-ray films of the gastrointestinal tract demonstrated an anastomosis between the proximal transverse colon and the ileum, which was consistent with resection of the right side of the colon and some of the terminal ileum. A blind loop of proximal transverse colon and a markedly dilated loop of small bowel were seen in the right upper quadrant.

Penicillin, 1.0 million units administered parenterally daily, produced moderate reticulocytosis (7 per cent) without change in hemoglobin or red cells. Parenteral vitamin B_{12} failed to produce a hematologic response. In addition, oral B_{12}, folic acid, streptomycin and achromycin failed to increase the red cell level.

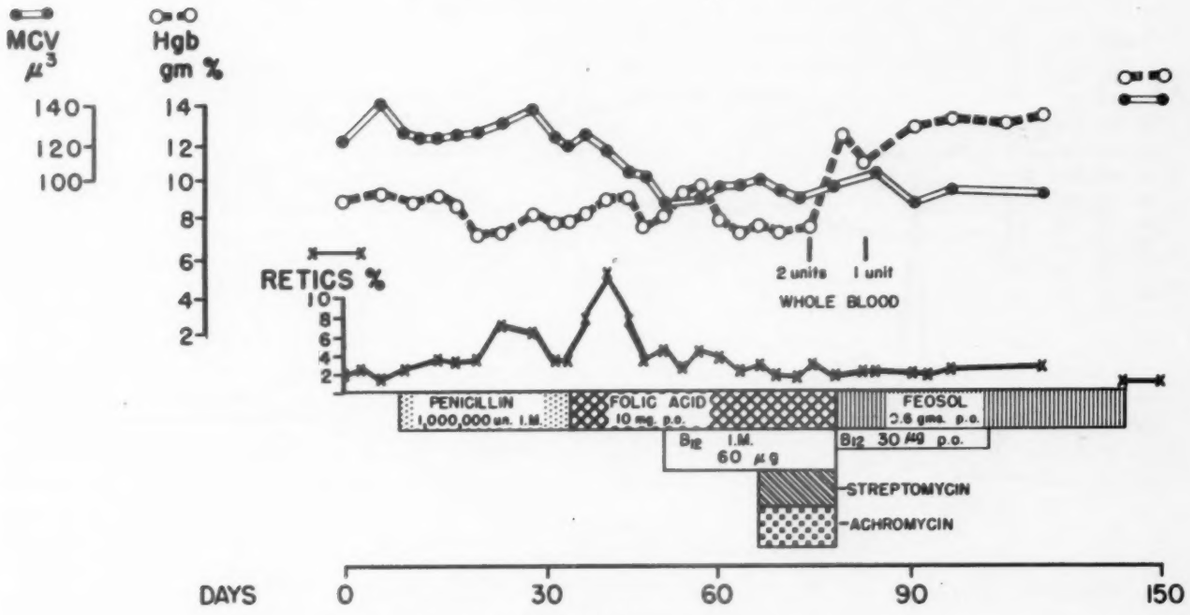

FIG. 3. Case 1. Blind loop anemia.

The hemoglobin fell gradually to 6.9 gm./100 ml., and the patient was given 1,500 ml. of whole blood, with improvement. The patient refused surgery and, upon discharge, was given oral iron medication. Her blood picture gradually returned to normal. Iron medication was discontinued after four months but hemoglobin levels have remained normal for two years. (Fig. 3.)

Comment. This patient demonstrated "blind loop anemia" with an intermediate type of erythropoiesis in the bone marrow. Histamine-fast achlorhydria, graying of the hair, cerebral symptoms, and an abnormal electroencephalogram were present,* together with a blood picture of pancytopenia with macrocytic anemia, all of which suggested pernicious anemia. However, the possibility of a non-Addisonian megaloblastic anemia was suggested by the presence of "modified" (intermediate) megaloblastic erythropoiesis. Further evidence in this direction was afforded by the low serum iron, and the x-ray findings of blind loops, apparently the result of an abdominal operation seven years previously. Proof of the non-Addisonian nature of the anemia was furnished by the failure of hematologic response to parenteral vitamin B_{12}, and by persistence of markedly impaired intestinal absorption of $Co^{60}B_{12}$ despite concomitant administration of a potent intrinsic factor preparation [*71,76,77,135–140,151*].

The mechanism of the megaloblastic anemia of the intestinal fistulas, diverticula and blind loop syndromes has not yet been fully delineated. Demonstrable absorptive defects are not necessarily related to the development of the anemia [*60,74,141*]. Thus only nine of nineteen patients with blind loop megaloblastic anemia [*60*] showed impaired absorption of fat; and such anemia can be produced experimentally in rats [*141*] without the production of defects in fat absorption. The anemia seems rather to depend on the accumulation and stagnation of intestinal contents in an antiperistaltic blind loop [*60,142*] with resultant changes in the gastrointestinal flora [*62b,143*]. The presence of abnormal microorganisms may lead to production and absorption of toxins [*144–146*], or to bacterial inactivation or binding of vitamin B_{12} [*146,147*]. Sterilization of the bowel by broad-spectrum antibiotics will usually [*66,68,69,75–79*], although not invariably [*69,71,72*], restore absorption of vitamin B_{12} to normal and afford remission. In occasional patients, the oral or parenteral administration of vitamin B_{12} or liver extract will produce hematologic remission [*61,63,65,70–74, 76*]; in other instances surgical extirpation of the affected loops will result in disappearance of the anemia, or will permit remissions previously induced by antibiotics or hematinics to persist despite withdrawal of such medications [*60,62a, 64,65,66,69,73,151*]. In the present patient folic acid, vitamin B_{12} and antibiotics were ineffective, and surgical correction was refused. Transfusions

* See reference [*156*].

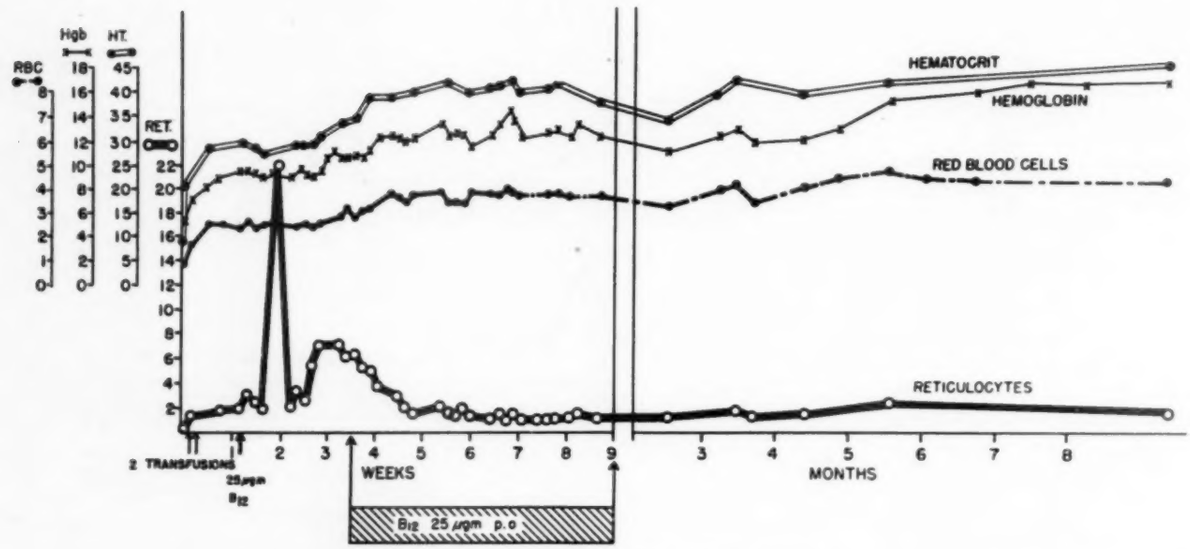

FIG. 4. Case II. Nutritional macrocytic anemia.

were necessary for improvement of the hematologic status. After subsequent oral iron medication, hemoglobin values returned to normal and have remained so for the past two years.

CASE II. M. S., a thirty-seven year old white housewife, entered The Mount Sinai Hospital on September 15, 1954, with a three-month history of weakness, easy fatigability, pallor and anorexia. For several weeks before admission marked exertional dyspnea had been noted; and for one week soreness of the tongue. There was no history of exposure to toxic agents. Profuse vaginal hemorrhages had been noted for two years until four months prior to admission. The past and family histories were non-contributory except that the patient's diet had been completely devoid of citrus fruits and almost devoid of greens and meats for many years. In the six months before admission she had further restricted her diet to crackers and tea, with a resultant 37-pound weight loss.

Physical examination revealed moderate obesity. There was marked pallor, and no icterus. The hair was brown and the ear size was normal. The tongue was not red but papillae were absent. The liver was palpable 2 cm. below the right costal margin. The rest of the examination, including neurological examination, was normal.

Initial laboratory findings (Table I) showed pancytopenia with macrocytic anemia. Blood smears showed moderate hypochromia and minimal poikilocytosis. Some of the granulocytes were hypersegmented. Bone marrow aspiration revealed hypercellularity, diminution in megakaryocytes and giant metamyelocytes. The predominant marrow cells were atypical megaloblasts (Fig. 2) which appeared morphologically intermediate between unequivocal megaloblasts and unequivocal normoblasts. The serum iron was 58 µg./100 ml. Gastric aspiration revealed free acid after histamine stimulation. X-rays of the gastrointestinal tract showed no abnormalities.

The patient received 1,000 ml. of whole blood on admission, and was given a regular hospital diet. Lobar pneumonia, diagnosed on the third hospital day, responded within three days to intramuscular penicillin therapy. On the eighth day the patient received a single oral dose of 25 µg. of vitamin B_{12}. Six days later the reticulocytes reached a peak of 22.4 per cent, and subsequently a slow rise in hemoglobin and hematocrit followed. (Fig. 4.) A second marrow aspiration, performed on the twentieth hospital day, revealed normoblastic erythropoiesis with a normal myeloid-erythroid ratio. On the twenty-second hospital day the patient began a course of oral vitamin B_{12}, 25 µg. daily. Two months later her hemoglobin was 14.8 gm./100 ml. (Fig. 4.)

Comment. This patient displayed a severe nutritional anemia with erythropoiesis of the intermediate megaloblast variety. A dramatic reticulocyte response, with conversion of erythropoiesis to the normoblastic variety and subsequent return of the blood values to normal, followed the oral administration of small amounts of vitamin B_{12} and a normal diet. The diagnosis of non-Addisonian megaloblastic anemia was suggested by the intermediate-megaloblast bone marrow picture, the relative lack of poikilocytosis in the smear [*2,3,37,59–61,81*], the low serum iron (ultimately attributed to dietary inadequacy and previous heavy men-

ses), and the presence of free gastric hydrochloric acid.

CASE III. J. C., an eighty-eight year old retired mechanic, entered The Mount Sinai Hospital on April 19, 1955, because of weakness, malaise and postprandial fullness and belching for three months. Since a diagnosis of pernicious anemia was made sixteen years previously, the patient had been treated at regular intervals with parenteral liver extract and, more recently, with vitamin B_{12}; three months before hospitalization he had become refractory to such therapy. Physical examination revealed pallor without icterus. The tongue was normal. A large mass filled the epigastrium and extended into the left upper quadrant of the abdomen.

Initial laboratory studies (Table 1) disclosed a macrocytic hypochromic anemia. The erythrocytes showed moderate aniso- and poikilocytosis. The serum iron was 48 μg./100 ml. Marrow aspiration revealed normal cellularity, adequate megakaryocytes, giant metamyelocytes, and both normoblastic and intermediate-megaloblastic erythropoiesis. Additional studies showed absence of free gastric hydrochloric acid. Guaiac reactions on the stools were persistently strongly positive. An x-ray examination showed diffuse gastric carcinoma.

Parenteral vitamin B_{12} failed to affect the blood or marrow picture. Laparotomy established a diagnosis of linitis plastica type of gastric carcinoma, with local and hepatic metastases.

Comment. This patient with long-standing pernicious anemia became refractory to parenteral vitamin B_{12}. At this time he was found to have gastric carcinoma, and guaiac-positive stools, intermediate-megaloblastic erythropoiesis was evident in the marrow.

Girdwood has seen two patients with pernicious anemia who ceased to respond to cyanocobalamin maintenance therapy after extensive gastric carcinoma developed; the bone marrow in each instance subsequently reverted to the megaloblastic state [*151*]. No statement was made as to the presence or absence of blood loss from the gastric lesions.

CASE IV. C. M., a fifty-nine year old housewife of Italian extraction, was admitted to The Mount Sinai Hospital because of weakness, fatigue, pallor, anorexia and exertional dyspnea, all of one month's duration. There was no history of paresthesias, diarrhea, glossitis or hemorrhagic tendency, and no history of operations. The hair had been gray for 24 years. The family history was non-contributory.

Physical examination revealed a pallid, icteric elderly white female. The tongue was pale and smooth. The liver was palpable 3 cm. below the right costal margin, and the spleen tip was just palpable. Neurological examination showed normal vibratory and proprioceptive sensations, and normal deep tendon reflexes.

Initial laboratory examination (Table 1) showed macrocytic anemia with moderate anisocytosis, poikilocytosis and polychromatophilia. Many red cells were hypochromic. Target and stippled cells were present. Reticulocytes numbered 6.1 per cent. Hypersegmented neutrophils were present. The serum bilirubin was 2.2 mg. per cent, of which 1.9 mg. per cent was indirect. Gastric analysis showed histamine-fast achlorhydria. Bone marrow aspiration revealed hypercellularity with intermediate megaloblastic erythropoiesis, giant myelocytes and metamyelocytes. Other studies, including glucose and vitamin A tolerance tests and x-rays of the gastrointestinal tract, were normal. The serum vitamin B_{12} level was less than 10 $\mu\mu$g./ml. Serum iron was 120 μg./100 ml. with total iron binding capacity of 403 μg./100 ml. per cent. Alkali-resistant hemoglobin was 4.8 per cent. Paper electrophoresis of the hemoglobin revealed only hemoglobin A.

Family studies showed no abnormalities in the blood of the patient's husband and in three of her seven children; the other four children, however, showed numerous target cells on blood smears, and alkali-resistant hemoglobin values of 3.6 per cent to 5.1 per cent. A test for absorption of oral vitamin B_{12} by the Glass *in vivo* technic [*129*] demonstrated failure of intestinal absorption of oral B_{12}. Accordingly, a diagnosis of pernicious anemia with concomitant thalassemia minor was made. The patient responded well to vitamin B_{12}, administered parenterally.

Comment. The pancytopenia, megaloblastic marrow, histamine-fast achlorhydria and low serum vitamin B_{12} suggested a diagnosis of pernicious anemia; this diagnosis was further suggested by the inability to absorb oral vitamin B_{12} in test doses, and by the clinical and hematological response to treatment with vitamin B_{12} (reticulocytosis, return of erythropoiesis to normoblastic type). At the same time, however, the marrow was intermediate rather than frankly megaloblastic; and the large number of target cells and the presence of hypochromia suggested concomitant loss, malabsorption or faulty utilization of iron. The finding of normal hemoglobin on filter paper electrophoresis and elevated alkali-resistant hemoglobin values in the patient and in four of seven children allowed the diagnosis of thalassemia minor.

COMMENTS

The occurrence of lines of red cell development which are morphologically intermediate

between the normal normoblastic variety and the Addisonian megaloblastic type is well documented. In nutritional macrocytic anemia such "megaloblasts with atypical features" were described by Fairley et al. [*19*], Trowell [*20*] and others [*26*]. Trowell distinguished the "nutritional macrocytic anemia megaloblast" (Fig. 2) as a more compact, smaller, thicker cell than the megaloblast of pernicious anemia (Fig. 1), and emphasized the absence of early eosinophilization, characteristic of pernicious anemia, in the megaloblast of nutritional macrocytic anemia [*20,24*]. Hotz and Rohr [*6*] described "macronormoblasts" in the marrow in sprue, in contrast to the frank megaloblasts of pernicious anemia. Of seventeen patients with sprue with macrocytic anemia studied by Cooke et al., thirteen showed "intermediate erythropoiesis" and only four had frankly megaloblastic erythropoiesis [*9*]. Innes noted that intermediate erythropoiesis persisted despite therapy in four patients with sprue treated with liver extract [*10*]. In thirty-three patients with sprue, Davidson et al. found only one classically megaloblastic marrow, and described in many of their other cases partial maturation with many nucleated cells "intermediate in appearance between megaloblasts and normoblasts" [*8,11*]. Davidson and co-workers also described intermediate erythropoiesis in intestinal strictures following tuberculous peritonitis [*67*], and Girdwood [*151*] and Dick [*72*] likewise noted "transitional" and intermediate megaloblastic erythropoiesis in the macrocytic anemia associated with intestinal blind loops and diverticula.

The only descriptions of intermediate megaloblasts in the American literature are those of Zuelzer [*50*] who described such findings in seven of fifteen cases of megaloblastic anemia of infancy, and of Lowenstein et al. [*46*] who noted their presence in pernicious anemia of pregnancy. Such intermediate forms have also been noted in partially treated pernicious anemia [*89*] and in pernicious anemia complicated by concomitant uremia, chronic infection or cancer [*133*].

We have observed and described in this report such modified (intermediate) megaloblasts in each of the four cases in this communication. During the study of these patients it was noted that a deficiency in serum iron (Cases II and III) or a condition associated with defective iron utilization (chronic infection, Case I [*153*], thalassemia minor, Case IV [*155*]) was present in each instance. Review of the literature revealed that intermediate megaloblastic erythropoiesis occurred in patients with pernicious anemia who were partially treated [*89,133*] or in whom marrow aspirations were obtained twelve to twenty-four hours after institution of therapy [*89*], i.e., when the serum iron levels were low [*148*].

Associated iron deficiency was also striking in many of the reported patients with nutritional megaloblastic anemia [*24,26,126*], and in other instances signs of iron deficiency appeared after hematologic response to vitamin B_{12} [*30*]. Similarly, in the blind loop syndrome, signs of overt iron deficiency often become evident after partial response to B_{12} or liver therapy [*73*]; in addition, the defective iron metabolism associated with chronic infection [*153*] is probably operative in the presence of the stagnant blind loops.

The defective iron metabolism associated with idiopathic steatorrhea has been documented by Badenoch and Callender [*150*]. We have noted modified (intermediate) megaloblasts in several patients with sprue; vitamin B_{12} and folic acid therapy produced considerable improvement in hematologic status, but normal hemoglobin values (14 gm./100 ml.) were obtained only after subsequent addition of iron therapy (imferon). (These patients will be reported in greater detail elsewhere.) Similar failure of folic acid to eliminate intermediate megaloblastic erythropoiesis was encountered in patient A. T. with the blind loop syndrome. (Case I.) Defects in iron stores or iron metabolism also are present in megaloblastic anemia of pregnancy [*46*] and in the chronic infection [*153*], carcinoma [*154*] or blood loss which may complicate pernicious anemia.

Analysis of these observations in the various conditions associated with non-Addisonian megaloblastic anemia suggests that intermediate megaloblasts are a distinctive and ubiquitous feature, and are a result of superimposition of defective iron stores or iron metabolism on vitamin B_{12} or folic acid deficiency. Presumably, defective iron metabolism hinders hemoglobinization of the megalocyte precursors, preventing full morphologic expression of the nuclear-cytoplasmic asynchronism associated with "true" megaloblastic erythropoiesis.

Although deficiencies in erythrocyte maturation factors other than vitamin B_{12} may provide a possible alternate explanation [*133*], we suggest

that modified megaloblasts result only when iron deficiency at the marrow level is superimposed in the course of megaloblastic erythropoiesis. Such a hypothesis allows facile explanation of the morphologically distinct form of abnormal erythropoiesis characterizing the non-Addisonian megaloblastic anemias and those instances of pernicious anemia complicated by blood loss, chronic infection, or carcinoma.

SUMMARY

1. Four cases are presented which illustrate the occurrence of modified or intermediate megaloblastic erythropoiesis in non-Addisonian macrocytic anemia.

2. The morphologic concept of intermediate megaloblasts is discussed, and its value in differentiating uncomplicated Addisonian pernicious anemia from other megaloblastic anemias is considered.

3. It is suggested that concomitant iron deficiency at the marrow level rather than a relative deficiency of vitamin B_{12} or other erythrocyte maturation factors is responsible for the occurrence of intermediate megaloblastic erythropoiesis.

ADDENDUM

Since completion of these studies, Monto, Kavanaugh and Rebuck (*Am. J. Clin. Nutrition*, 6: 105, 1958) described five additional subjects with nutritional megaloblastic anemia, and Krasnow, Walsh, Zimmerman and Heller (*Arch. Int. Med.*, 100: 870, 1957) noted megaloblastic anemia in seven patients with alcoholic cirrhosis. Mollin, Booth and Baker (*Brit. J. Haematol.*, 3: 412, 1957) documented the variable effect of antibiotics on $Co^{60}B_{12}$ absorption in patients with the megaloblastic anemia of the blind loop syndrome. Further, Pedersen, Lund, Ohlsen and Kristensen (*Lancet*, 1: 448, 1957) demonstrated partial megaloblastic erythropoiesis in elderly achlorhydric patients with combined B_{12} and iron deficiency. Serum iron levels averaged 76 μg. per 100 ml. in their subjects with partial megaloblastic erythropoiesis, 120 μg. per 100 ml. in total megaloblastic erythropoiesis.

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Agranulocytosis Following Administration of Phenothiazine Derivatives*

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CHLORPROMAZINE [10-(gamma-dimethylaminopropyl)-2-chlorophenothiazine] was introduced in 1952 for the treatment of psychiatric disease. Soon thereafter occasional reports of agranulocytosis following the use of this and related drugs began to appear in the literature [*1–15*]. Over twenty instances of agranulocytosis and eight deaths attributable to chlorpromazine have been reported.

The pathogenesis of granulocytopenia induced by drugs has been the subject of wide speculation. An immunologic mechanism is undoubtedly responsible for some types of agranulocytosis but it is evident that other mechanisms also are involved in this hematologic reaction. It seems appropriate in a study of the pathogenesis of agranulocytosis to delineate the development and natural course of the syndrome. An opportunity to do so was presented by the occurrence of eighteen instances of agranulocytosis in sixteen patients treated at the Milwaukee County Hospital for Mental Diseases with phenothiazine derivatives. The observations to be reported herein embrace the relationship of time and dosage to development of agranulocytosis, the mode of onset, morphologic aspects of the bone marrow, immunologic studies, effects of readministration of the drug and the clinical management of the syndrome.

CLINICAL DATA

Clinical data on the patients with agranulocytosis are summarized in Table 1. While we have no accurate record of the total number of patients at the Milwaukee County Hospital for Mental Diseases (H. M. D.) who have received a phenothiazine compound, a conservative estimate suggests that over 3,000 persons have received these drugs since they were introduced. The development of agranulocytosis on eighteen occasions implies that this reaction may not be of rare occurrence. Of the sixteen patients affected, four were men. This is of interest because all of the instances of agranulocytosis previously recorded occurred in women. All of our patients, as well as those previously recorded by others, were Caucasian. The fact that about 8 per cent of the patients who were treated with the drug are Negroes suggests a diminished susceptibility to agranulocytosis in this racial group. A similar experience was reported by Lambo [*16*] who observed no agranulocytosis or jaundice in 1,600 Negroes in Nigeria, treated with chlorpromazine. The causes of these sex and racial differences are not clear. In our series, the total dosage of chlorpromazine administered before granulocytopenia occurred ranged between 2 gm. (Case 12) and 112 gm. (Case 14, Fig. 1A). The number of days of treatment with phenothiazine varied from ten days (Case 13) to 401 days (Case 14, Fig. 1B).

The manner of onset of agranulocytosis in patients who received chlorpromazine was quite characteristic. (Table 1.) In Cases 1, 2a, 4, 7, 8, 10, 12, 15 and 16, agranulocytosis was recognized after symptoms of infection developed. However, in nine instances (Cases 2b and c, 3, 5, 6, 9, 11, 13 and 14) agranulocytosis was recognized by routine periodic blood check in asymptomatic individuals. Thus the signs and symptoms of agranulocytosis, if any, were principally those of infection of the respiratory tract. However, cellulitis (Case 15), proctitis (Case 15) and bacteremia (Case 1) also were seen. There was no clinical evidence of allergy, such as hay fever, urticaria, asthma or angioneurotic edema.

Peripheral Blood and Bone Marrow Picture. In

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TABLE I

CLINICAL DATA

Case No.	Sex and Age (yr.)	Diagnosis	Drug	Cumulative Dosage (gm.)	Total Duration of Treatment/ Days	Other Drugs	Symptoms	Lowest White Blood Cell Count	Treatment	Outcome
1, J. M.	F, 35	Paranoid schizophrenia	Chlorpromazine	26.0	43	None	Sore throat T = 104°F.	800	ACTH, penicillin	Recovered
2a, M. V.	F, 50	Schizophrenia	Chlorpromazine	18.5	121	Serpasil Reserpine benadryl®	Sore throat	1,050	ACTH, penicillin	Recovered
b	....	.....	Promazine	5.025	21		None	1,500	Penicillin	Recovered
c	....	.....	Prochlorperazine	13.7	42	None	None	3,100	None	Recovered
3, H. M.	M, 52	Paranoid schizophrenia	Chlorpromazine	11.2	27	None	None	1,300	ACTH, penicillin	Recovered
4. F. N.	M, 26	Catatonic schizophrenia	Chlorpromazine	17.6	45	None	Sore throat T = 102°F.	2,000	ACTH, penicillin	Recovered
5, E. E.	F, 57	Chronic alcoholism, cerebral degeneration	Chlorpromazine	24.8	42	Reserpine	None	750	ACTH, penicillin	Recovered
6, E. F.	F, 49	Schizophrenia	Chlorpromazine	28.6	42	Reserpine	None	2,200	Penicillin	Recovered. Chlorpromazine restarted forty days later, 200 mg. daily. No untoward reaction after one year observation.
7, E. S.	M, 55	Involutional psychosis	Chlorpromazine	14.4	57	Ritalin	Sore throat	1,120	Penicillin	Recovered
8, A. B.	F, 49	Paranoid schizophrenia, diabetes mellitus	Chlorpromazine	6.6	33	None	Sore throat, T = 101°F., lethargy, dehydration, coma	500	ACTH, penicillin, insulin, glucose, saline intravenously	Died Diabetic acidosis
9, D. P.	F, 41	Depressive psychosis	Chlorpromazine	11.4	43	None	None	1,250	ACTH, erythromycin	Recovered
10, M. H.	F, 65	Catatonic schizophrenia	Chlorpromazine	21.9	73	Digitalis, ritalin	T = 103°F., pharyngitis with ulceration, bronchopneumonia, abdominal distention	200	Penicillin	Died
11, A. M.	F, 52	Schizophrenia, disseminated lupus erythematosus	Chlorpromazine	8.5	36	Prednisone, leukocyte extract, metrazol, digitalis, mercuhydrin	None	1,300	Prednisone, erythromycin, tetracycline	Recovered
12, M. K.	F, 43	Cerebral degeneration, epilepsy	Chlorpromazine	2.0	25	Dilantin, phenobarbital, reserpine	Sore throat, T = 102°F.	1,100	Penicillin, achromycin, erythromycin	Recovered
13, K. F.	F, 47	Schizophrenia	Chlorpromazine, perphenazine	28.5 0.3	13 11	None	None	1,600	Penicillin	Recovered
14, P. G.	M, 47	Hebephrenic schizophrenia	Chlorpromazine, promazine	65.6 36.6	318 83	None	Ankle edema	3,400	None	Recovered
15, A. L.	F, 64	Involutional psychosis, melancholia	Chlorpromazine, prochlorperazine	3.75 .225	25 18	Meprobrate	Infection in finger, lymphangitis, jaundice	1,500	Penicillin, chloramphenicol, erythromycin, neomycin	Recovered
16, S. H.	F, 49	Dementia praecox, paranoid	Chlorpromazine	4.1	37	None	Pharyngitis, fever, pustular dermatitis	2,150	Penicillin	Recovered

those patients in whom it was possible to follow the leukocyte count before the development of agranulocytosis we observed a latent period of twenty to thirty-five days during which time the leukocytes remained approximately normal or lowest point varied between 200 (Case 10) and 3,500 per cu. mm. (Case 14).

The bone marrow picture is depicted in Table III and in Figure 3. At the height of leukopenia there was a highly selective aplasia of

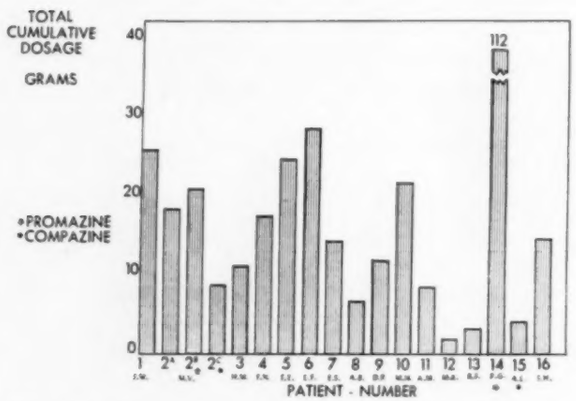

FIG. 1A. Relationship of onset of agranulocytosis to dosage of chlorpromazine (or related drug as indicated).

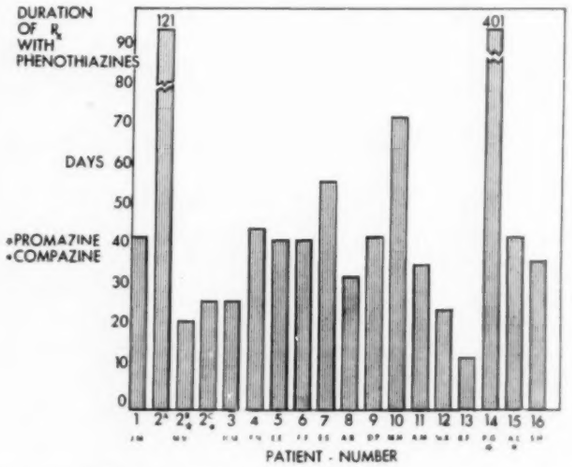

FIG. 1B. Relationship of onset of agranulocytosis to duration of treatment with chlorpromazine (or related drug as ndicated).

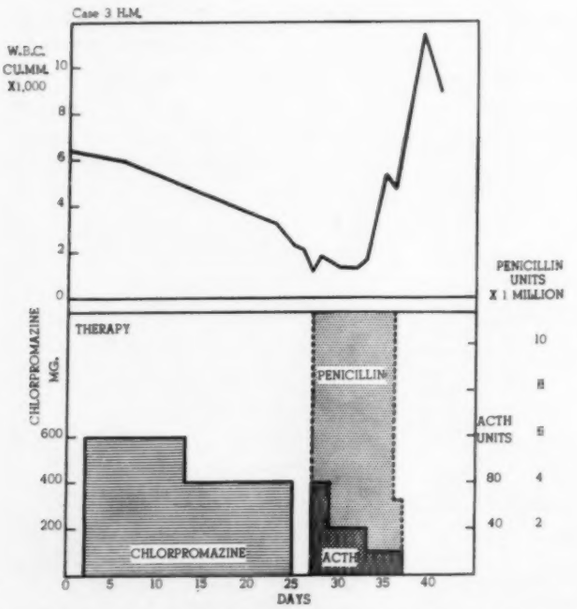

FIG. 2A. Case 3. Serial leukocyte counts during therapy with chlorpromazine prior to onset of agranulocytosis.

showed very gradual reduction in number. (Fig. 2.) When agranulocytosis developed there was a precipitous decrease of the leukocyte count, which reached its lowest level two to five days after the decrease had begun. The fully developed blood picture of this group of patients (Table II) showed a marked granulocytopenia with normal numbers of erythrocytes, platelets and reticulocytes. The total white cells at the

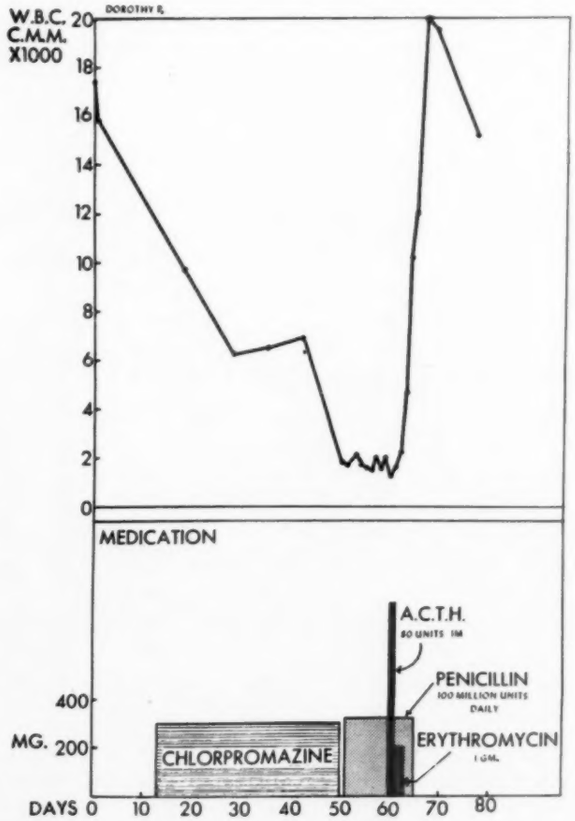

FIG. 2B. Case 9. Serial leukocyte counts during therapy with chlorpromazine prior to onset of agranulocytosis.

the cells of the granulocytic series (Cases 1, 3, 5a, 7 to 9) but no involvement of the erythropoietic or thrombopoietic centers. (Fig. 3A.) During early stages of recovery, progranulocytes made their appearance. (Fig. 3B.) As healing progressed, early and then late myelocytes were seen. (Fig. 3C.) When recovery occurred, maturation extended to the metamyelocyte level and band forms. (Fig. 3D.) Thus, if only one observation of the marrow had been made during the stage of extreme leukopenia, the erroneous impression might be gained of "maturation arrest" at the progranulocyte or myelocyte level. As pointed out by Plum [*17*] and by Dameshek [*18*], stages in the healing process of a previously aplastic marrow may simulate the appearance of arrested development in the maturation of marrow cells.

With discontinuance of the drug, granulopoiesis was resumed in five to ten days. The peripheral blood stream at this stage frequently showed an increase in monocytes which provided a favorable prognostic sign. During the early stages of marrow recovery, occasional myelocytes and metamyelocytes appeared in the peripheral blood. Recovery from that point on was rapid, often with a mild leukocytosis between the tenth and fifteenth days. In Case 11, lupus erythematosus (L.E.) cells, previously known to be present, disappeared from the peripheral blood and bone marrow during the period of granulocytopenia and reappeared with recovery.

Immunologic Studies. While there was no clinical evidence for peripheral destruction of leukocytes, extensive immunologic studies were performed on the serums of all the patients in this series. In these experiments we added to the patient's serum varying quantities of chlorpromazine and a suspension of leukocytes obtained from a compatible donor or from the patient following recovery. These systems were observed grossly and by phase contrast microscopy for leukagglutination. In no instance did leukagglutination occur. Leukolysins were sought by incorporating complement with the serum-chlorpromazine-white cell mixtures and by doing serial leukocyte counts at intervals. There was no significant diminution in the number of leukocytes and therefore no *in vitro* evidence of white cell lysis. A similar failure to detect antileukocyte antibodies was reported by Rotstein, Frick and Schiele [*8*].

The occurrence of agranulocytosis in a patient known to have disseminated lupus erythematosus (Case 11) is of interest for several reasons. This woman was treated previously with an extract made from normal leukocytes [*19*], which may have resulted in isosensitization. (Fig. 4.) Also, lupus erythematosus is frequently associated with abnormal antibodies to erythrocytes, platelets and clotting proteins, and may itself be a manifestation of "auto-immunization" to collagen tissue. However, attempts to demonstrate leukagglutinins or leukolysins in this patient's serum by a variety of technics produced completely negative results.

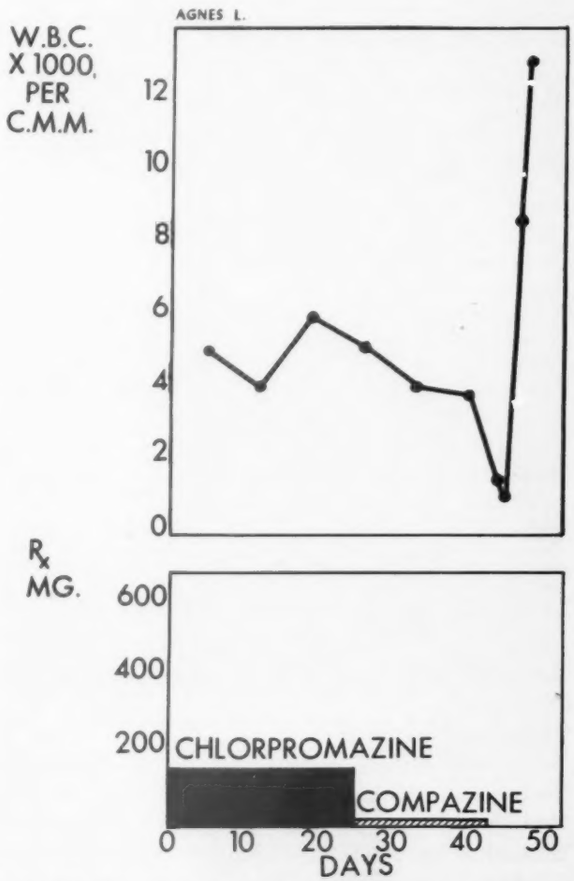

FIG. 2C. Case 15. Serial leukocyte counts during therapy with chlorpromazine prior to onset of agranulocytosis.

Effects of Readministration. Further evidence of the non-immunologic nature of this reaction is derived from observation of the effect of readministration of the drug or a closely related compound. In Case 6 (E. F., Fig. 5) chlorpromazine was readministered in lower dosage for one year without repetition of untoward hematologic reaction. A similar experience was reported by Yules and Baker [*9*]. In another

TABLE II
PERIPHERAL BLOOD COUNTS

Data	Case No.																	
	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Hemoglobin (gm./100 ml.)	13	10.5	15	—	14.5	12.5	10	12	12	12	11	11	11	9.5	13.5	11	10.5	14
Red blood cells (million/cu. mm.)	4.19	3.89	5.50	—	4.48	4.51	3.50	5.45	3.29	3.83	3.34	3.35	3.75	3.01	4.75	—	3.69	—
White blood cells (per cu. mm.)	800	1,050	1,500	3,100	1,300	2,000	750	2,200	1,950	750	1,200	200	1,300	1,100	1,600	3,500	1,150	2,150
Segmented forms (%)	0	0	1	37	0	0	2	8	0	0	0	0	2	1	2	0	0	2
Band forms (%)	0	1	0	11	0	0	0	17	0	0	0	0	6	1	2	3	0	5
Eosinophils (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Basophils (%)	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphocytes (%)	100	97	92	47	98	44	86	68	78	96	99	99	85	95	96	75	85	77
Monocytes (%)	0	1	3	5	2	55	12	7	22	4	1	1	5	2	0	21	6	16
Plasma cells (%)	0	1	0	0	0	1	0	0	0	0	0	0	2	1	0	0	9	0
Metamyelocytes (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Thrombocytes (per cu. mm.)	167	305	93	—	230	103	104	—	280	211	220	—	254	158	453	120	192	—
Reticulocytes (%)	1.2	1.5	—	—	1.8	0.6	1.0	—	1.2	—	—	—	—	1.6	—	—	3.2	—

NOTE: 0 = None present.
— = Note done.

TABLE III
BONE MARROW DIFFERENTIAL COUNTS

Data	Case No.															
	1	2a	2b*	3	4	5a	5b*	7	8	9	11	12*	13	14*	15	16*
Myeloblast	0	0.2	2	0.4	1.7	3.0	2.0	0.7	1.4	1	0	0.6	1	3.5	0	0
Progranulocyte	7.4	40.0	2	4.2	21.3	3.6	3.2	0.7	0.7	1	0.5	1.2	14	37.5	9.5	2.3
Neutrophilic myelocyte	0.6	1	29	4.0	15.7	0.4	8.8	9.7	0	8	11	13.6	3	9	0	53.3
Neutrophilic metamyelocyte	0	0	19	0.8	0.7	0	22.6	1.7	0	1	3	21.8	0	0.25	0	3.3
Neutrophilic band forms	0	0	41.5	3.2	0.3	0	35.2	0	0	0	1.5	11.6	0	0.5	0	0.3
Neutrophilic segmented forms	0	0	2.5	1.6	0	0	9.6	0	0	0	0	4.2	0	0	0	0
Eosinophilic myelocyte	0	0	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0
Eosinophilic segmented forms	0	0	0	0	0	0	0	0	0	0	0	0.4	0	0	0	0
Reticulum cell	0	0	0	0	0	0.6	2.6	0	3.0	0	1	0.4	0	3	3.5	0.3
Lymphocyte	51.6	4.2	0	31.6	17.7	3.2	3.6	35.0	78.6	1	24	24.4	46	7.25	57	17.3
Plasma cell	2	0.2	0	2.2	4.0	3.2	1.6	2.0	6.4	5	0	2.0	1	2.5	3.5	3.3
Pronormoblast	0	0	0	0	0.7	2.2	0.4	4.7	1.4	23	2.5	0	0	2	1	1
Basophilic normoblast	0	7.4	0	1.0	2.3	22.0	1.0	11.0	0.7	40	13	4.0	0	0.5	3	2
Polychromatophilic normoblast	26.4	46.4	0	46.0	30	44.2	5.4	27.0	3.0	20	38	8.0	33	24.25	21.5	15.3
Orthochromic normoblast	9.6	0.2	2.0	4.0	1	15.8	4.0	6.7	1.4	0	4.5	6.6	2	9.75	0.5	1.7
Megakaryocyte	1.4	0.6	0	0.8	0.7	1.2	0	1.0	4.7	0	0.5	0.2	0	0	0.5	0
Monocyte	1	0	0.5	0.2	5	0.2	0	0	0	0	0	0	0	0	0	0
Unclassified	0	0	0	0	0	0	0	0	0	0	2.5	0	0	0	0	0
Basophiles	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0	0.3

* Bone marrow taken during stage of recovery.

patient (M. V., Fig. 6) granulocytopenia followed therapy with a cumulative dosage of 18.5 gm. of chlorpromazine given over 121 days. One year following recovery, promazine was given. Agranulocytosis again developed in twenty-one days during which time 5.025 gm.

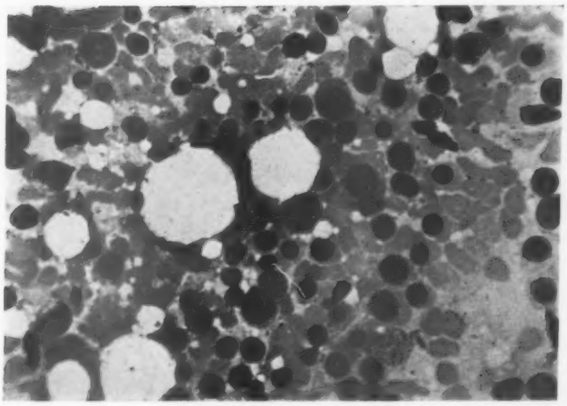

FIG. 3A. Bone marrow at the height of agranulocytosis. There is virtually complete absence of all granulocyte precursors. Original magnification, × 1200.

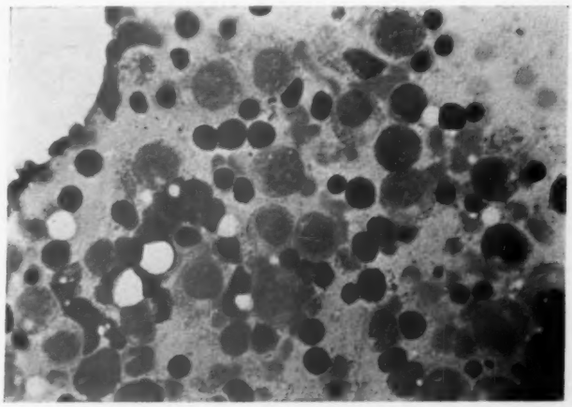

FIG. 3B. Bone marrow shortly after onset of recovery. Maturation extends to progranulocyte and early myelocyte level. Original magnification, × 1200.

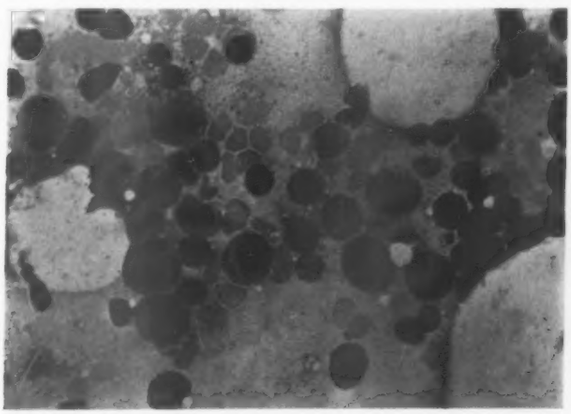

FIG. 3C. Bone marrow during recovery phase. Many myelocytes with toxic granulation are seen. There is still absence of mature granulocytes. Original magnification, × 1200.

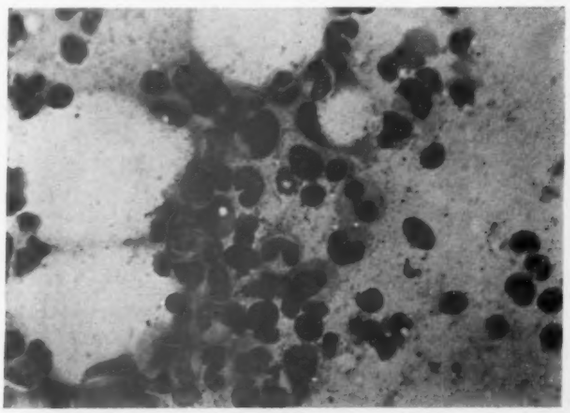

FIG. 3D. Bone marrow after recovery. Return of band forms and metamyelocytes. Original magnification, × 1200.

were given. One year later, agranulocytosis again developed for a third time following the administration of 13.7 gm. of prochlorperazine given over forty-four days. In all of these instances the hematologic reaction was delayed and not explosive. In spite of this delayed reaction, readministration of any member of the phenothiazine group for an extended period to a patient who has had agranulocytosis attributed to this family of drugs seems unwise.

CASE REPORTS

CASE 1. J. M. (M.C.G.H. 475224), a thirty-five year old woman, was hospitalized for paranoid schizophrenia. She received chlorpromazine continuously for forty-four days, in a cumulative dosage of 26 gm. At this time pharyngitis developed, with an oral temperature of 104.6°F. Leukocytes numbered 850 per cu. mm. with lymphocytes 96 per cent and monocytes 4 per cent. Bone marrow showed depression of the granulocytic series with absence of maturation past the myelocyte level. Normoblast and megakaryocyte development were normal. She received adrenocorticotropic hormone (ACTH) gel 100 units, and penicillin 10,000,000 units intramuscularly daily. Leukocytes increased gradually and complete recovery was evident six days later.

CASE 2 (Fig. 6). M. V. (M.C.G.H. 475801), a fifty year old woman, was hospitalized for dementia praecox. On January 5, 1955, she received chlorpromazine 50 mg. daily. The dosage was increased to 200 mg. on February 23, and to 600 mg. daily on April 19, 1955. She also received reserpine and serpasil® during this time. On March 5, 1955, a leukocyte count of 11,800 per cu. mm. was recorded. On May 6, 1955, the patient complained of pharyngitis and was found to have a low grade fever. At this time a white blood cell count of 1,700 per cu. mm. was found with segmented neutrophils 1 per cent, band forms 1 per cent and lymphocytes 98 per cent. The

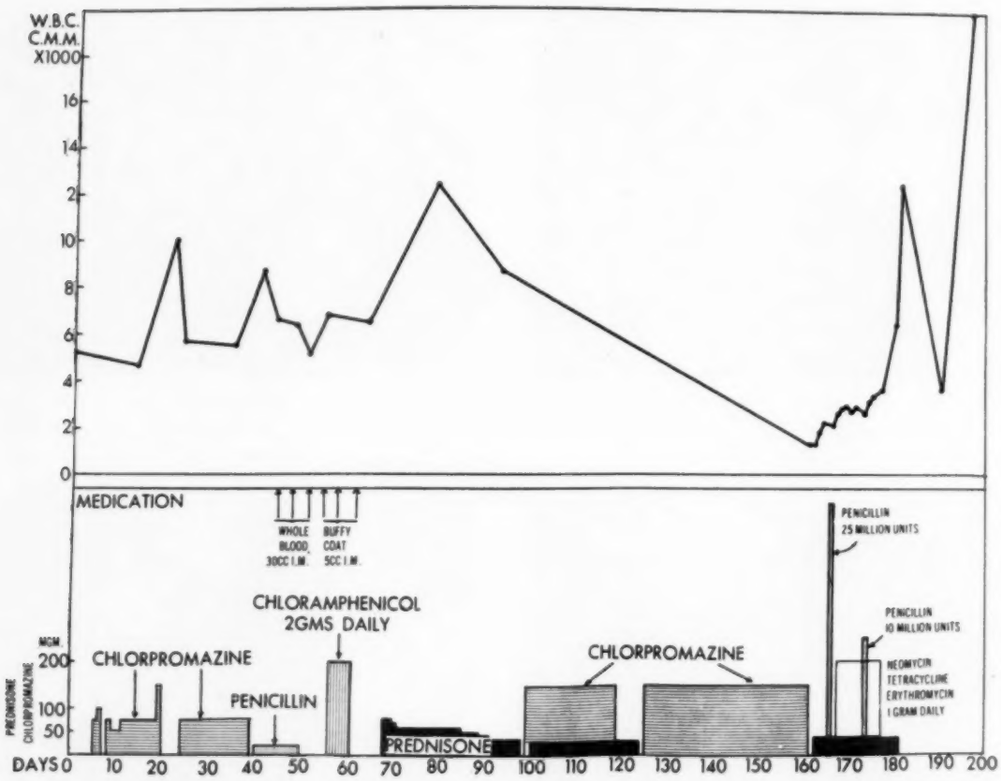

FIG. 4. Case 11. Course of agranulocytosis in a patient with disseminated lupus erythematosus previously treated with leukocyte "buffy coat" preparation.

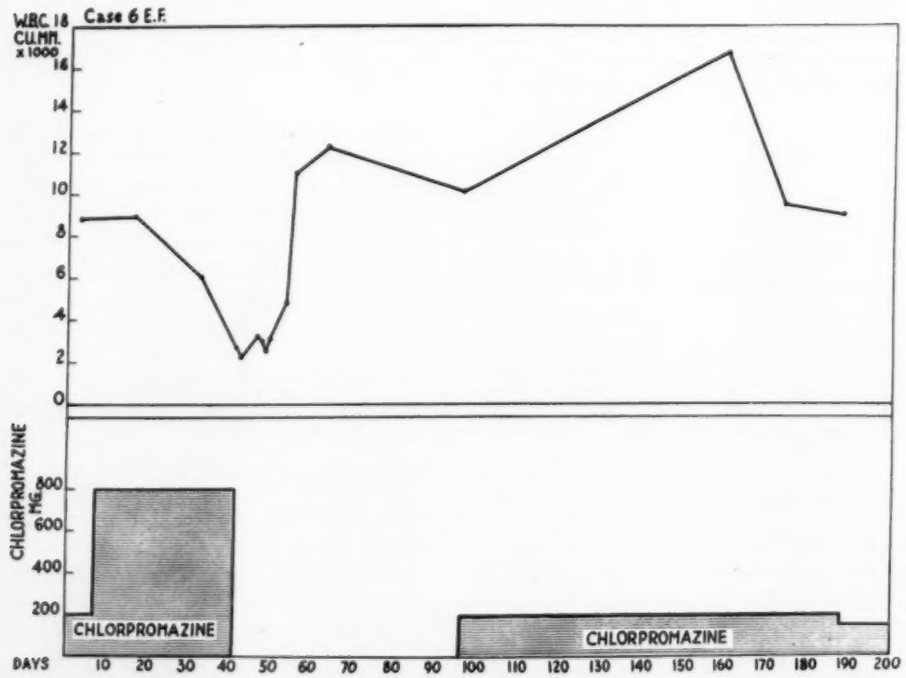

FIG. 5. Case 6. Effect of readministration of chlorpromazine in lower dosage after recovery from agranulocytosis.

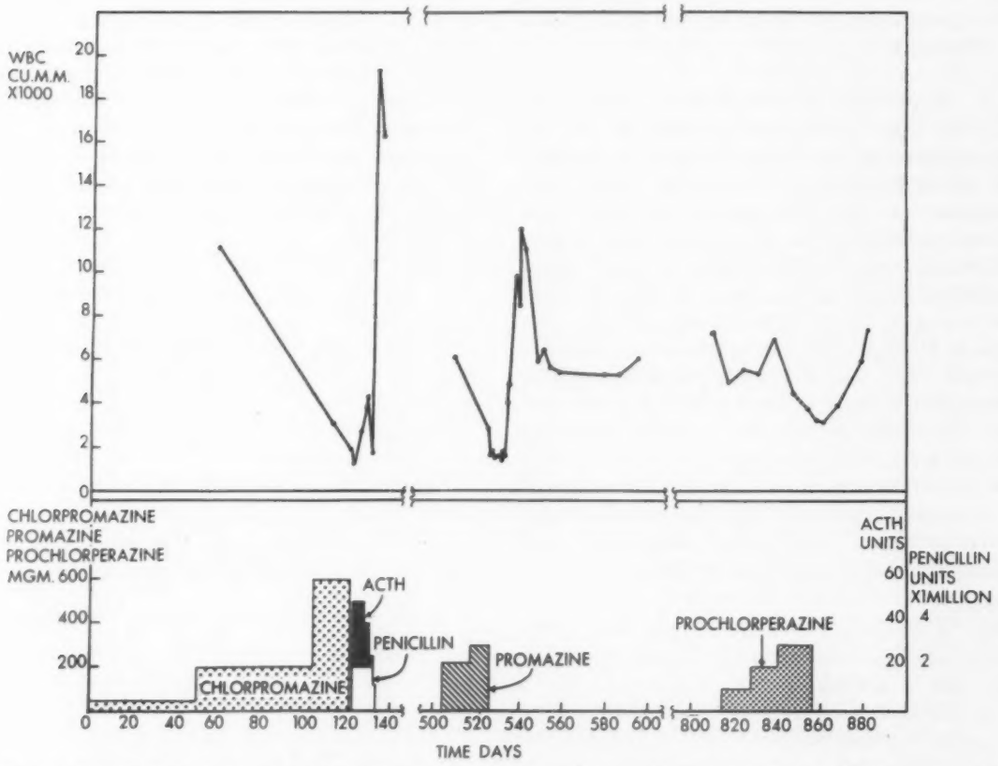

FIG. 6. Case 2. Effects of readministration of promazine and prochlorperazine to a patient recovered from agranulocytosis following chlorpromazine.

bone marrow showed no granulocytes past the myelocyte stage.

Adrenocorticotropic hormone gel was administered in a daily dosage of 50 units intramuscularly together with penicillin 2,000,000 units intramuscularly daily. The leukocytes increased to 2,300 four days later and eleven days after admission the white blood cell count was 19,300 per cu. mm. The leukocyte count remained normal during the next period of observation.

One year later promazine was started in the amount of 225 mg. a day. The leukocyte count on May 28, 1956, was 6,100 and the dosage was increased to 300 mg. daily. On June 12, 1956, the white blood cell count was 2,800 per cu. mm with segmented forms 17 per cent, band forms 14 per cent and lymphocytes 69 per cent.

On readmission to Milwaukee County Hospital (M.C.G.H. 502676) there were no significant physical findings. The leukocytes numbered 1,650 per cu. mm. with 9 per cent segmented forms, 3 per cent band forms and 88 per cent lymphocytes. The bone marrow showed a marked increase in fatty tissue with a decrease in granulocytes. The cellularity consisted chiefly of normoblasts, lymphocytes and an occasional progranulocyte. The patient was given penicillin 20,000,000 units intramuscularly daily. She made an uneventful recovery, the peripheral blood and bone marrow returning to normal in ten days.

On March 29, 1957, the patient was started on prochlorperazine (compazine) 100 mg. daily. On April 12 the daily dosage was increased to 200 mg. and on April 24, to 300 mg. Weekly leukocyte counts showed a gradual drop in white blood cells. Prochlorperazine was discontinued on May 10 after a cumulative dosage of 13.7 gm. The lowest leukocyte count recorded on May 13 was 3,100 per cu. mm. Thereafter the leukocytes again increased to 7,350 per cu. mm. No treatment was given at this time.

CASE 3 (Fig. 2). H. M. (M.C.G.H. 476951), a fifty-two year old white man with paranoid schizophrenia, was given chlorpromazine. Twenty-five days later, when 11.2 gm. of this drug had been administered, the leukocytes on a routine count were noted to be 3,200 per cu. mm. Chlorpromazine was discontinued but the white blood cell count continued to drop to 1,200 per cu. mm. two days later. There were no symptoms and no significant physical signs. The bone marrow aspirate showed a depression of the granulocytic series with cellularity confined largely to the myelocyte level. He was given penicillin 10 million units daily, and adrenocorticotropic hormone gel 80 units daily. The leukocytes increased to normal

values and he was discharged on June 1, 1955, with a white blood cell count of 8,950 per cu. mm. and a normal differential count.

CASE 4. F. N. (M.C.G.H. 477882), a twenty-six year old white man with catatonic schizophrenia, was given chlorpromazine 400 mg. daily while at the Hospital for Mental Diseases. Thirty-five days after administration of chlorpromazine was begun the leukocytes numbered 5,250 per cu. mm. with a normal differential count. Ten days later the white blood cells numbered 2,000. At this time the patient complained of a sore throat and chlorpromazine was immediately discontinued. On examination, the temperature was 102°F. and there was purulent tonsillitis and pharyngitis. The tip of the spleen was just palpable. The bone marrow showed a depression of the granulocytic series with few cells more mature than the myelocyte level. The patient received penicillin 10 million units, and adrenocorticotropic 80 units daily. The leukocyte count returned to normal and full physical recovery occurred ten days later.

CASE 5. E. E. (M.C.G.H. 481275), received chlorpromazine 800 mg. daily in a cumulative dosage of 248 gm. over a period of thirty-eight days. Serial leukocyte counts showed a drop from 7,900 to 2,650 over a twenty-four-day period. At the end of this time pharyngitis developed, cardiac enlargement and a temperature of 102°F. The liver was palpated 4 cm. below the costal margin and the inguinal lymph nodes were enlarged and purulent. The leukocytes dropped to 750 per cu. mm., with 2 per cent segmented forms, 86 per cent lymphocytes and 12 per cent monocytes. The bone marrow showed selective depression of the granulocytic series and absence of forms older than myelocytes. Normoblasts and megakaryocytes were normal. Penicillin 3 million units, and adrenocorticotropic hormone gel 40 units, were given daily. The leukocytes increased in five days and remained normal following the patient's discharge from the County General Hospital.

CASE 6 (Fig. 5). E. F. (M.C.G.H. 482839), a forty-nine year old white woman with schizophrenia, received chlorpromazine 800 mg. daily for about forty days. During this time a leukocyte count obtained every two weeks remained normal. On August 18, 1955, she entered the County Hospital for surgical repair of an inguinal hernia. Routine admission blood count showed the leukocytes to be 2,200 per cu. mm. with 8 per cent band forms, 17 per cent monocytes. The bone marrow showed selective depression in the granulocyte series with cellular development as far as the myelocyte level. Chlorpromazine was discontinued. Penicillin or adrenocorticotropic hormone were not given. In ten days the leukocyte count became normal. In September the patient had the required surgery without complication and was sent back to the Hospital for Mental Diseases on October 12, when the leukocytes remained normal. Forty days later (October 14) chlorpromazine was given in a dosage of 200 mg. daily. This drug has been given continuously until August, 1957, in a dosage of 100 mg. daily. There has been no evidence of granulocytopenia while on lower doses of chlorpromazine. On the last recorded blood count taken on July 26, 1956, the leukocytes were 10,800 per cu. mm.

CASE 7. E. S. (M.C.G.H. 488661), a fifty-five year old white man, was hospitalized for involutional psychosis. On September 22, 1955, he was given chlorpromazine 100 mg. daily, which was increased to 400 mg. daily on October 10. During this time the leukocyte count remained normal. On November 14 he complained of severe sore throat and was found to have a temperature of 102°F. On admission to Milwaukee County Hospital, the leukocytes numbered 1,850 per cu. mm. with lymphocytes 78 per cent and monocytes 22 per cent. The bone marrow showed absence of granulocyte precursors, except for a few myelocytes.

Therapy consisted of penicillin, 12 million units by combined intravenous and intramuscular routes. Corticosteroid therapy was not used in this patient. He made an uneventful recovery, and eight days after chlorpromazine was discontinued the leukocytes numbered 7,250 per cu. mm. with a normal number of granulocytes.

CASE 8. A. B. (M.C.G.H. 491833), a forty-nine year old woman was given chlorpromazine 200 mg. daily, beginning December 7, 1955. On January 7, after a cumulative dosage of 6,600 mg., fever and a sore throat developed and she was given penicillin 4 million units daily. The spleen and liver were each enlarged 4 cm. below the costal margin. The leukocytes numbered 750 per cu. mm. with 96 per cent lymphocytes and 4 per cent monocytes. The urine showed 4 plus glucose and 4 plus acetone. The patient was in profound diabetic acidosis in addition to the severe pharyngitis associated with granulocytopenia. Treatment consisted of 80 units of ACTH, and 4 million units of penicillin daily. She did not respond to insulin and intravenous fluids and died two days following admission. There was no autopsy.

CASE 9 (Fig. 2C). D. P. (M.C.G.H. 500102), a forty-one year old woman with depressive psychosis, received chlorpromazine 300 mg. daily for forty days in a total dosage of 11,400 mg. She had no symptom, but on routine blood check, taken on May 11, the white blood cells numbered 1,800 per cu. mm. with 14 per cent band forms, 3 per cent segmented forms, 81 per cent lymphocytes and 2 per cent monocytes. The total leukocyte count remained unchanged for the next twelve days but all granulocytes disappeared from the peripheral blood during this time.

The bone marrow showed a virtual absence of all granulocyte precursors, but normal erythropoiesis and megakaryopoiesis remained. The patient was given penicillin 12 million units intramuscularly daily. Although she remained afebrile and asymptomatic for eleven days, the granulocytopenia persisted unchanged. For this reason she was given ACTH 80 units intramuscularly. On the twelfth day the leukocytes count was normal. The patient was dismissed with a white cell count of 10,200 per cu. mm. and a normal differential count.

CASE 10. M. H. (M.C.G.H. 506954), a sixty-five year old white woman with paranoid psychosis, was started on a regimen of chlorpromazine 300 mg. daily on June 30, 1956, and ritalin® 180 mg. daily on July 3, 1956. The white blood count was 8,600 per cu. mm. on June 11, and on June 23 was 5,100 per cu. mm. On the evening of August 12 routine observation showed the temperature to be 103°F. She was unable to relate her symptoms. On physical examination the patient appeared to be acutely ill. The posterior pharynx was ulcerated and the base of the tongue was covered with necrotic tissue. The lungs showed bilateral fine crackling rales and bronchial breath sounds. The abdomen was distended, but no organs or masses were palpable. The leukocyte count on the morning of August 13 showed 2,750 white cells per cu. mm. with lymphocytes 99 per cent and monocytes 1 per cent. A blood count repeated eight hours later showed a drop in leukocytes to 200 per cu. mm. The bone marrow was composed almost entirely of fat cells. Occasional groups of lymphocytes, plasma cells, normoblasts and megakaryocytes were present. No granulocyte precursors were seen. Treatment was immediately started with penicillin 2,600,000 units, and chloramphenicol 1,000 mg. daily. She died on the afternoon of the second hospital day. Autopsy was not performed.

CASE 11 (Fig. 4). A. M. (M.C.G.H. 510188), a fifty-two year old white woman, had been hospitalized at the Hospital for Mental Diseases since April, 1956, with schizophrenia. While in the hospital the patient had chronic symptoms consisting of weakness, fatigue, diarrhea and arthralgia. Physical findings demonstrated a precordial friction rub and a mitral presystolic murmur. The diagnosis of disseminated lupus erythematosus was confirmed by a positive lupus erythematosus (L.E.) cell preparation. She was initially treated with a preparation made from leukocytes from a compatible donor, according to the method of Kurnick [*19*]. There was no objective or subjective improvement in one month and treatment with prednisone was begun on June 30, 1956. The initial dosage was 60 mg. and the drug was reduced stepwise to a maintenance of 30 mg. daily. She also received isoniazid hydrochloride 300 mg. daily. In August abscesses and decubiti on both buttocks developed, treated with incision and drainage. They did not heal, however, and the prednisone was gradually discontinued on August 21. On August 21, 1956, chlorpromazine was started 150 mg. daily, with a total cumulative dose of 5.4 gm. Other drugs used during this period were metrazol® 120 mg. daily, digitalis 0.1 gm., and mercuhydrin® 2 cc. intramuscularly weekly. Routine blood count taken on September 26 showed 1,800 leukocytes per cu. mm. with segmented neutrophils 7 per cent, band forms 3 per cent, lymphocytes 85 per cent and monocytes 5 per cent. Chlorpromazine was immediately discontinued. On physical examination, the patient was alert, afebrile and cooperative. There was a crescendo presystolic rumble at the cardiac apex. The liver and spleen were both palpable 1 cm. below the costal margin. There were healed decubiti on both buttocks and 2 plus edema of both ankles. The bone marrow showed depletion of all granulocytic precursors and consisted entirely of normoblasts and lymphocytes. Buffy coat preparations from heparinized bone marrow showed no lupus erythematosus (L.E.) cells. Treatment was begun with prednisone 50 mg. daily, which was subsequently diminished to 30 mg. daily. She also received penicillin 10 million units intravenously, erythromycin and tetracycline, 1 gm. of each daily by mouth. During the remaining ten days of hospitalization the leukocyte count slowly increased and on October 16 was restored to 6,400 per cu. mm. with a normal differential count.

CASE 12. M. K. (M.C.G.H. 512599) was hospitalized because of cerebral degeneration associated with idiopathic epilepsy. She had been treated with chlorpromazine 150 mg. daily, from October 5 to October 25. She had also been given phenobarbital, dilantin® and reserpine. On October 25 the patient complained of sore throat and had a temperature of 102°F. Physical examination showed enlarged red tonsils with a follicular exudate. The leukocyte count was 1,100 per cu. mm. with segmented neutrophils 1 per cent, band forms 1 per cent, lymphocytes 95 per cent, monocytes 2 per cent and 1 per cent unclassified cells. A bone marrow was obtained on November 5, when the leukocytes had increased to 4,150 per cu.mm. The marrow showed diminished cellularity with predominant lymphocytosis. There was, however, an abundance of young granulocytes and a normal number of normoblasts and megakaryocytes. The patient was given penicillin 10,000,000 units, achromycin and erythromycin 1 gm. intravenously daily, to November 2. On this date chloramphenicol was given 1 gm. intramuscularly daily, and gamma globulin 20 ml. into each buttock. Corticosteroid therapy was not administered. The leukocytes had begun to rise on November 3 and by November 6 the white cell count was completely normal. On November 24 the patient was discharged asymptomatic.

CASE 13. K. F. (M.C.G.H. 521406) was treated at the Milwaukee County Hospital for Mental Diseases

for mental illness. Chlorpromazine was started on February 1, 1957, and was given continuously until February 13, 1957, to a total dosage of 28.5 gm. It was discontinued because of a skin eruption and facial edema. On February 23 administration of perphenazine (trilafon®) was started in a dosage of 8 mg. three times a day. This was discontinued on March 6, 1957, when a routine blood count disclosed 2,600 leukocytes per cu. mm. The patient was asymptomatic. There was no clinical evidence of infection and physical examination revealed no abnormalities. On admission to the Milwaukee County Hospital, the hemoglobin and erythrocyte values were within normal limits. The leukocytes numbered 1,600 per cu. mm. with band forms 2 per cent, segnented neutrophils 2 per cent and lymphocytes 96 per cent.

This woman received only penicillin. On the day following admission the leukocytes began to increase and complete restoration to normal was noted on March 14, when the white cells numbered 5,200 per cu. mm. with band forms 19 per cent, segmented neutrophils 2.0 per cent, metamyelocytes 2 per cent, myelocytes 2 per cent, basophils 2 per cent, lymphocytes 48 per cent and monocytes 8 per cent. Since her discharge back to the Hospital for Mental Diseases this patient has remained completely well.

Case 14. P. G. (M.C.G.H. 528617) had been committed to the Milwaukee County Hospital for Mental Diseases for more than twenty years because of hebephrenic schizophrenia. He was unable to relate a history. On December 5, 1955, chlorpromazine was started 200 mg. daily. This drug was given continuously and with no untoward effects until October 18, 1956. He was given no phenothiazine until March 9, 1957, when administration of promazine was started 200 mg. daily. On May 4 the dosage was continued to 600 mg. daily, and on May 8 it was further increased to 1,000 mg. daily. While under observation at the Hospital for Mental Disease there were no toxic effects upon the peripheral blood. On June 1 he was sent to the Milwaukee County Hospital because of edema of the ankles and albuminuria. There were no further symptoms and the patient was afebrile. A routine admission blood count showed 3,400 leukocytes per cu. mm. with band forms 3 per cent, lymphocytes 75 per cent, monocytes 21 per cent and metamyelocytes 1 per cent. The bone marrow showed considerable granulocytic activity. No antibiotics and no corticosteroids were given. The patient remained asymptomatic and the leukocyte count returned to normal four days after admission.

Case 15 (Fig. 2C). A. L. (M.C.G.H. 533112), a sixty-four year old white woman, was hospitalized because of involutional psychosis with melancholia. From June 26, 1957, to July 21, 1957, she was treated with chlorpromazine 150 mg. daily; from July 21, 1957, to August 8, 1957, she received prochlorperazine (compazine) 15 mg. daily. During this time she also received meprobromate.

On August 5, 1957, an infection of her left index finger was noted. On August 8, 1957, she was admitted to Milwaukee County Hospital with a temperature of 103.4°F., orally, lymphangiitis of her left arm and axilla, purulent rhinitis and icterus. A blood count on August 9 revealed the leukocytes to be 1,500 per cu. mm. with lymphocytes 85 per cent, monocytes 5 per cent, plasma cells 9 per cent and unclassified cells 1 per cent. The bone marrow showed absence of granulocytic maturation past the myelocyte stage. Treatment was begun with intravenous penicillin 10,000,000 units every twelve hours, tetracyline 250 mg. every four hours and intramuscular penicillin 300,000 units every six hours. On August 13, 1957, these drugs were discontinued and a combination of chloramphenicol, erythromycin and neomycin was begun and continued until August 27, 1957.

On August 9 the patient had an episode of auricular fibrillation with pulmonary edema, hepatomegaly and neck vein distention; this responded promptly to oxygen and digitalis. On August 12, 1957, bilateral ischiorectal abscesses were noted. These drained spontaneously and healing progressed rapidly. On August 14 she had an episode of diarrhea, with gram-positive cocci on direct smear of the stool, and on August 15, thrombophlebitis developed at the site of a cut-down in one leg.

Following the agranulocytosis, a leukocytosis with immature myeloid cells in the peripheral blood developed and persisted until August 28, when the blood count returned to normal. The total serum bilirubin was 3.66 mg. per 100 ml. of which 1.75 mg. reacted directly. The cephalin-cholesterol flocculation test was 3 plus in forty-eight hours. The serum alkaline phosphatase was 2.7 B.L. units (normal = 2.3). The bromsulphalein retention was 11.8 per cent after forty-five minutes, the serum cholesterol was 140 mg. per 100 ml. with 46.5 per cent esters, and the total serum protein was 7.0 gm. per 100 ml. with 2.7 gm. albumin and 4.3 gm. globulin. The abnormal liver function studies reverted to normal in one week. As the infections subsided, the patient became afebrile and she has made a gradual recovery.

Case 16. S. H. (M.C.G.H. 532116), a forty-nine year old white woman, was hospitalized because of dementia praecox, paranoid type. On June 19, 1957, administration of chlorpromazine 200 mg. twice daily was begun. On July 26, 1957, after a cumulative dose of 4,100 mg. of this drug, pharyngitis, a pustular dermatitis and a temperature of 103°F. developed. The initial blood count showed the leukocytes to be 2,150 per cu. mm. with 5 per cent band forms, 2 per cent segmented neutrophils, 77 per cent lymphocytes and 16 per cent monocytes. Bone marrow examination showed a deficiency in mature granulocytic cells, past the early myelocyte stage with

toxic granules. She was treated with 10,000,000 units of penicillin intravenously each day for two days, then 2,400,000 units of penicillin daily intravenously for two days, then 2,400,000 units of penicillin daily intramuscularly in divided doses. The pharyngitis and dermatitis gradually cleared, and her blood and bone marrow returned to normal.

COMMENTS

Consideration of the development of granulocytopenia following drugs has disclosed well marked characteristics which distinguish at least three clinical varieties of this reaction. In the first group, administration of the offending drug will result in a predictable reduction of granulocytes in all persons, a reduction which may be quantitatively related to the amount of drug administered. By virtue of this myelodepressant activity, some of these substances, such as myleran,® 6-mercaptopurine and triethylene melamine, have been employed in the therapy of leukemia. Knowledge of the other two types of reaction has accumulated since amidopyrine was shown to cause agranulocytosis by Madison and Squier [*20*] in 1933. These early observations on the reaction to aminopyrine showed it to be of low incidence, of explosive onset, and that readministration of even minute quantities of the drug led to prompt recurrence. This points to an immunologic reaction, possibly characterized by lysis of the granulocytes in the peripheral blood and destruction of granulocyte precursors in the bone marrow. Further evidence of the immunologic mechanisms was provided by Dameshek and Colmes [*21*] who demonstrated a marked granulocytopenic response to the intradermal administration of a very small amount of amidopyrine which had been incubated with the serum of a sensitized individual. Many subsequent workers demonstrated leukagglutinins and leukolysins in the serum of persons sensitive to amidopyrine when the serum was incubated with the drug and brought into contact with leukocyte suspensions [*22*].

The third type of agranulocytosis was characterized by a course in which there was no abrupt onset or violent response to readministration such as occurred in agranulocytosis following amidopyrine. Thus, granulocytopenic reactions to the antithyroid compounds rarely appear before the tenth day of treatment and only after large doses are given [*23*]. Cases of this sort are associated with depletion of granulocyte precursors in the bone marrow [*24*]. This may be related to an increasing concentration of the offending drug in the bone marrow [*25*] with possible intoxication of proliferating myeloid cells. Granulocytopenia following the phenothiazines seems to be of this type. Because the great majority of patients who receive these drugs escape this reaction, it is likely that individual biochemical or enzymatic idiosyncrasies might play a role in the development of this syndrome. While these series of compounds are not related chemically, both have in common the presence of sulfur in their molecules. It has been demonstrated that sulfur-containing amino acids are important to granulocytic proliferation. Parker and Kracke [*26*] described a depletion in glutathione concentration in bone marrow and blood in benzol-induced granulocytopenia. More recently, Weisberger [*27*] demonstrated that leukopenia associated with nitrogen mustard treatment could be prevented by the prior administration of L-cystine. It was further shown [*28*] that leukocytes incorporated S-35 labelled L-cystine into their cytoplasm, indicating the importance of this amino acid in leukopoiesis. Whether certain sulfur-containing compounds block the incorporation of this essential amino acid by selective competition is highly speculative.

It is important to recognize the reversible nature of agranulocytosis induced by drugs. When the drug is stopped and the patient is protected from infection, recovery will probably occur. Death is most commonly due to infection and the principal aim of therapy therefore is to prevent exposure of the patient to virulent organisms. To this end, our patients are kept in isolation and all attendants, nurses and physicians attending the patient are appropriately gowned and masked. During the period of agranulocytosis, antibiotics are administered. Penicillin has been used most extensively and, when necessary, the combined use of chloramphenicol and erythromycin has provided protection against the staphylococcous. "Myelostimulatory" substances have not been considered essential. Adrenocorticotropic hormone (ACTH) and cortisone were administered to patients in Cases 1 to 9, but not in the subsequent patients. There was no clear difference in the clinical course of the two groups, suggesting that the corticosteroids have no particular value as marrow stimulators when the marrow is already depleted of granulocytes. Prevention of agranulocytosis in cases in which the use of

potentially toxic drugs is essential can best be accomplished by using the smallest effective doses, checking the leukocyte count at weekly intervals, and instructing the patient and attendants to report promptly fever, sore throat or malaise.

Despite the present widespread use of chlorpromazine in a variety of disorders, all of our cases of agranulocytosis and most of those reported in the literature have occurred in the mentally ill. Possible exceptions are the cases of Hodges and LaZerte [5] and of Yules and Baker [9]. The former was a woman apparently without mental disease in whom agranulocytosis occurred following the administration of 50 mg. of chlorpromazine daily over a three-week period. There is some question as to whether or not this patient had chronic lymphocytic leukemia. The latter was an elderly woman known to have arthritis, but no reported mental disease. This overwhelming incidence of agranulocytosis in psychiatric patients is almost certainly more than coincidental and is probably explained by the large amounts of this drug used over long periods of time. Whether or not such an abnormality might be peculiar to mental illness is presently under study.

SUMMARY AND CONCLUSIONS

1. Clinical and hematologic findings are presented in eighteen cases of agranulocytosis which followed treatment with chlorpromazine.

2. Granulocytopenia was of gradual onset and followed prolonged treatment with a large cumulative dose of chlorpromazine.

3. Granulocytopenia is seen much more frequently in women than in men.

4. During the height of leukopenia, the bone marrow is devoid of granulocyte precursors, suggesting temporary aplasia. During recovery, there is a gradual reappearance of granulocyte precursors which may simulate maturation arrest if first observed at this stage.

5. There was no clinical evidence of allergy in the cases studied. No leukagglutinins or leukolysins were demonstrated *in vitro*. While individual idiosyncrasy to the drug has not been ruled out, there is no evidence to support an immunoallergic mechanism as the pathogenetic factor.

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Tricuspid Regurgitation Masquerading As Mitral Regurgitation in Patients with Pure Mitral Stenosis*

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TRICUSPID insufficiency develops in patients with chronic rheumatic heart disease when there is destruction of leaflet tissue or when, under a variety of circumstances, the right ventricle dilates. The diagnosis should be suggested by persistent right-sided heart failure accompanied by pulsating neck veins and liver. Partial confirmation may be provided by x-ray evidence of right atrial enlargement and ventricularization of the right atrial pressure waves at the time of catheterization [*1*].

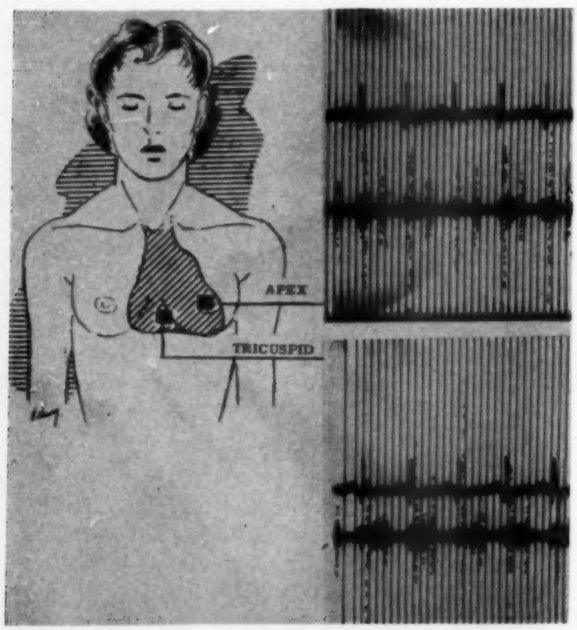

FIG. 1. Phonocardiogram taken at the apex and tricuspid area in a twenty-six year old woman with mitral stenosis and tricuspid regurgitation. A grade 3 murmur during systole was noted at both areas in association with a presystolic murmur.

Although the lesion is accompanied by a systolic murmur which should be heard best at the lower end of the sternum or at the fourth left interspace, auscultation may not be helpful diagnostically The murmur often is obscured by the associated valve defects which dominate the clinical findings, or it is erroneously attributed to a non-existent lesion.

This report concerns the latter problem. It records the fact that when there is marked right ventricular hypertrophy with clockwise rotation of the heart in patients with tricuspid insufficiency and mitral stenosis, the tricuspid murmur may extend toward the apex and may be mistaken for mitral insufficiency. It also examines the pathophysiologic background against which this misconception is most apt to arise. Finally, it emphasizes the importance of the error when patients are being evaluated for mitral commissurotomy, and discusses the methods by which the mistaken diagnosis may be avoided.

MATERIAL AND METHODS OF STUDY

The study concerns five patients with chronic rheumatic heart disease, ranging in age from twenty-six to fifty-seven years. Table I records the essential clinical manifestations.

The anatomic and functional characteristics of both the mitral and tricuspid valves were determined at the time of intracardiac surgery in all but one patient. (Table II.) One of the patients came to autopsy.

A right ventriculogram, according to the technic outlined by Lehman [*2*], was performed in three patients. (Table III.) In one of these a left ventriculogram also was obtained. Three of the patients were

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TABLE I

CLINICAL FINDINGS IN FIVE PATIENTS WITH PURE MITRAL STENOSIS AND TRICUSPID REGURGITATION

Patient	Age (yr.)	Sex	Symptoms						Signs*																			
									Extra Cardiac								Cardiac											
											Neck Veins		Liver										Systolic Murmurs					
			Fatigue	Exertional Dyspnea	Hemoptysis	Orthopnea	Paroxysmal Nocturnal Dyspnea	Pulmonary Edema	Cyanosis	Distention	Pulsation	Enlargement	Pulsation	Ascites	Ankle Edema	PMI	M_1	Diastolic Rumble	Opening Snap	Apex		Xyphoid Process		Left Axilla	
V. G.	26	M	+	+	+	+	+	0	++	+++	+++	+++	+	+	0	VI LIS AAL	Normal	++	0	++ Harsh		+++ Harsh		++ Harsh	
M. Y.	53	F	+	+	+	+	+	+	0	++	+	+	0	0	0	V LIS MC-AAL	Sharp	++	0	+++ Harsh		+++ Harsh		++ Blowing	
L. C.	43	F	+	+	0	+	+	0	0	0	0	+++	0	0	++	V LIS MC-AAL	Sharp	+++	+	+++ Blowing		+++ Blowing harsh		+(+) Blowing	
M. M.	26	F	+	+	0	+	0	0	0	0	+	++(+)	0	0	++	V LIS MC-AAL	Sharp	+++	0	+++(+) Harsh		++(+) Blowing		+++ Harsh	
I. T.	47	F	+	+	0	+	+	0	0	+++	++	+++	++	0	+++	V LIS MC-AAL	Sharp	++	+	+++ Musical		+++ Musical		++ Musical	

* On the basis of 1 to 4 plus grading.
PMI—point of maximum impulse.
VI LIS—sixth left intercostal space.
V LIS—fifth left intercostal space.
AAL—anterior axillary line.
MC-AAL—between midclavicular and anterior axillary line.

subjected to catheterization. (Table IV.) In two a combined right and left heart catheterization was performed; in the remaining patient only the left side of the heart was examined. In all patients, logarithmic phonocardiograms were taken at all valve areas before and after mitral commissurotomy. (Fig. 1.)

TABLE II

OPERATIVE FINDINGS IN FOUR PATIENTS

Patient	Mitral Valve		Tricuspid Regurgitation	Right Atrial Size
	Area (cm.²)	Regurgitation		
V. G.	0.7	0	+++	+++
M. Y.	0.8	0	+++	+++++
L. C.	0.6	0	++	++
M. M.	0.6	0	+++	+++
I. T.	0.7	0	*	+++++

* Not explored because of development of hypotension

TABLE III

RESULTS OF CARDIAC VENTRICULOGRAPHY (DIRECT OPACIFICATION) OF THE VENTRICULAR CHAMBERS)

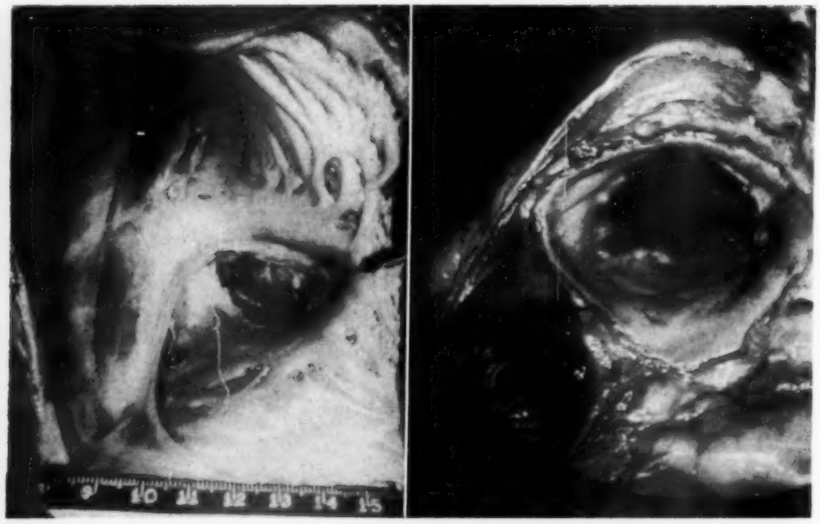
Patient	Ventriculogram*	
	Left	Right
V. G.	0	++++
M. Y.	Not done	++++
L. C.	Not done	+++

* On the basis of 1 to 4 plus grading.

RESULTS

The clinical manifestations of these patients included marked fatigability and exertional dyspnea, with orthopnea or paroxysmal nocturnal dyspnea. Without exception the cervical veins were considerably engorged, and pulsated in all but one. Although the liver was enlarged in each patient it was seen to pulsate in only two.

The auscultatory evidence for mitral stenosis was unequivocal and with but one exception consisted of both a sharp first sound and a mid-late diastolic rumble. A loud, rather harsh systolic murmur was heard at the apex of the heart in all the patients. The murmur was heard with maximal intensity at the lower left sternal border and at the xiphoid process, and was transmitted mainly toward the axilla and, on



2A 2B

FIG. 2. Postmortem specimen from a patient with mitral stenosis and tricuspid regurgitation demonstrating (A) the huge capacity of the right atrial chamber, and (B) the marked dilatation of the tricuspid valve orifice.

occasion, toward the base of the heart. In either locale its intensity was noticeably diminished. Generally, the murmurs were not altered appreciably by exercise nor did inspiration or change in the patient's position produce a constant or predictable increase in intensity.

The electrocardiographic patterns were indicative of right ventricular hypertrophy in every instance. Atrial fibrillation was present in three patients, and a normal sinus rhythm in two.

Roentgen examination of the heart revealed considerable increase in the size of the right atrium and ventricle. The left atrium in each of the patients was considered only moderately enlarged, and in no instance was there unequivocal evidence of left ventricular enlargement. During surgery direct examination of the heart confirmed these impressions, particularly in relation to the size of the right atrium. In one patient a postmortem examination confirmed the presence of an aneurysm of the right atrium. (Fig. 2.)

Catheterization of the left side of the heart revealed marked elevation of the left atrioventricular gradient filling pressure in all but one patient. In addition, the pulmonary arterial

TABLE IV

CARDIAC CATHETERIZATION DATA IN THREE PATIENTS WITH PURE MITRAL STENOSIS AND TRICUSPID REGURGITATION

Patient	Cardiac Index (L./min./m²)	Pressures (mm. Hg)					LA-LV Ventricular Filling Gradient (mm. Hg)
		Left Ventricle	Left Atrium	Pulmonary Artery	Right Ventricle	Right Atrium	
M. M.	*	112/0	(26)	88/45 (68)	90/0–8	(2)	24
I. T.	1.1	90–108/3–6	(19)	63–86/28–32 (47)	60–88/8–12	(10)	12
M. Y.	...	124–138/2–8	(26)	.....	.....	....	23

NOTE: Figures in parentheses represent means.
* Blood samples technically not satisfactory.

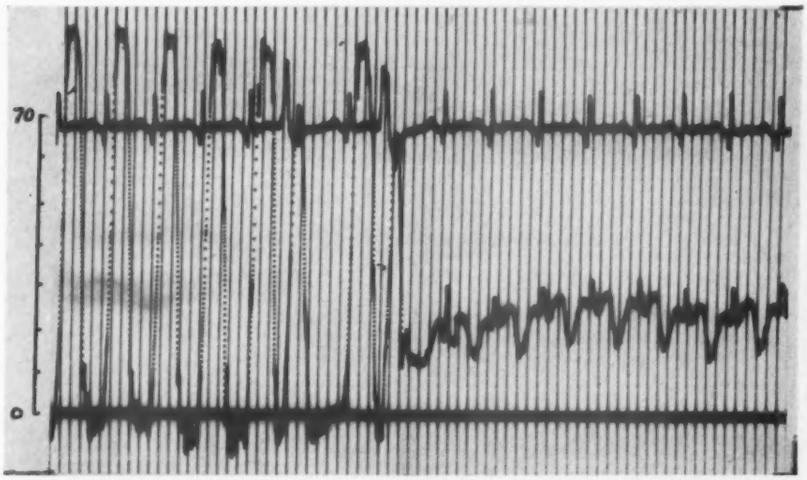


FIG. 3. Continuous tracing obtained during catheterization of the left side of the heart as the catheter is withdrawn from the left ventricle into the left atrium. The patient had a tight mitral stenosis without regurgitation and the surgeon acknowledged a 3 plus jet at the tricuspid valve during systole. The left ventricular filling gradient measured 24 mm. Hg.

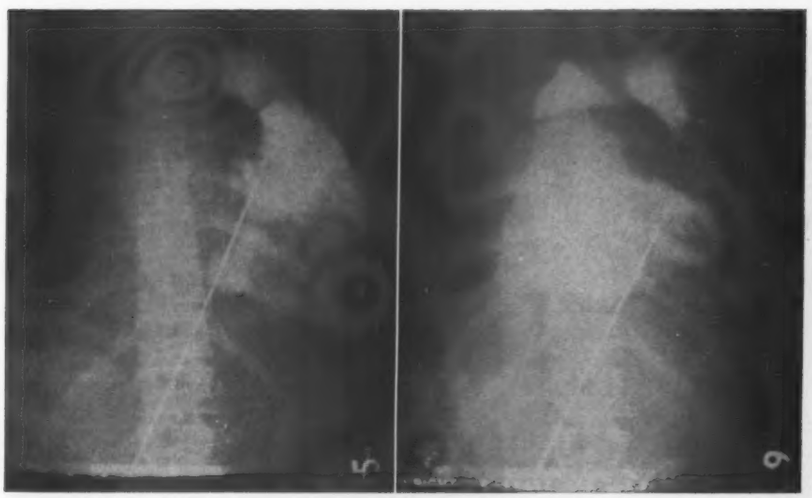


FIG. 4. Right cardiac ventriculography in patient V. G. Films taken a few seconds apart reveal reflux of dye from a dilated right ventricle across the tricuspid valve into a huge right atrium. The opacification of the pulmonary artery is well seen.

pressures were considerably elevated in every patient in whom catheterization of the right side of the heart was performed. (Fig. 3.) The estimated functional mitral valve areas were less than 1 sq. cm. (Table II.) Ventriculography revealed a reflux of dye across the tricuspid orifice in all the patients in whom this study was performed. (Figs. 4, 5 and 6.) There was no reflux across the mitral valve in a patient in whom the dye was injected into the left ventricle. (Fig. 7.)

Marked mitral stenosis and tricuspid insufficiency were found in every patient at the time of surgical exploration. In one case, no attempt was made to enter the right atrium because of systemic hypotension but a thrill was felt over the right atrial wall during ventricular systole.

COMMENTS

No unusual difficulties were experienced in recognizing mitral stenosis in these patients. The additional diagnosis of tricuspid insufficiency was suggested but not established by the presence of peripheral venous congestion and an engorged or pulsating liver. Considerable hesitancy, however, arose in holding this lesion responsible for the apical systolic murmur since

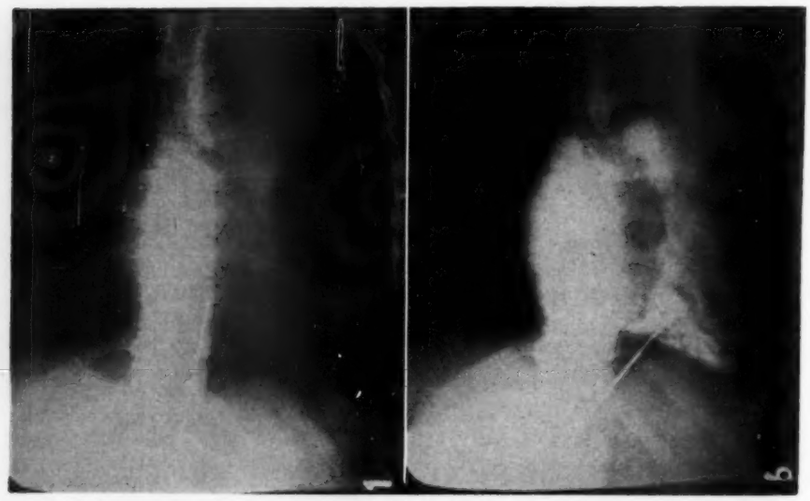


FIG. 5. Right cardiac ventriculography in patient L. C. with mitral stenosis and tricuspid regurgitation. Films taken at rapid intervals after direct injection of dye into the right ventricle, reveal immediate opacification of the right atrium. This does not occur in the presence of a competent tricuspid valve. Note the position of the tricuspid valve.

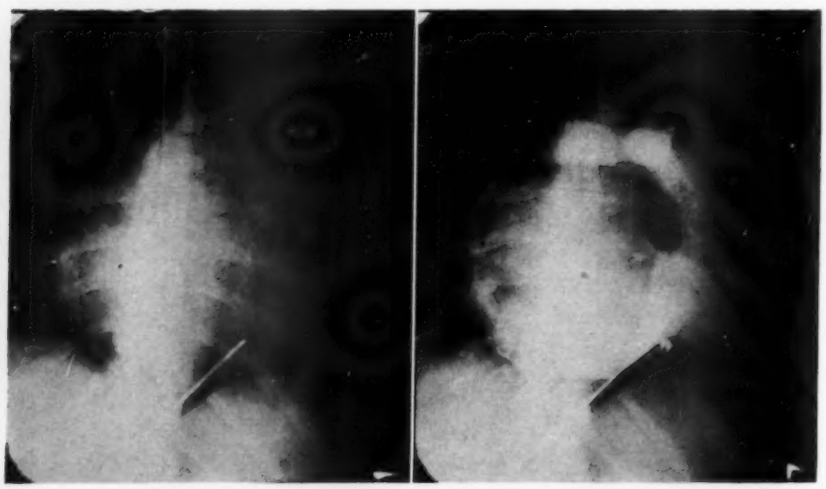


FIG. 6. Right cardiac ventriculography in patient M. Y. A film taken a few seconds after injection of dye into the right ventricle reveals marked opacification of the right atrium. A small amount of the dye also passed into the ventricular muscle.

many features of this murmur suggested that it was caused by mitral insufficiency. Thus a problem arose as to whether incompetence of the tricuspid, the mitral, or both valves accompanied the mitral stenosis. The various methods of resolving such a question were clarified by reviewing the present clinical experience.

The history may be helpful. In each of the patients studied the slow devolutionary pattern culminated in right ventricular failure. This persisted for unusual periods of time without resulting in death and was suggestive of tricuspid insufficiency since right-sided heart failure in mitral insufficiency generally develops after the left ventricle has decompensated, and therefore is a poorly tolerated and often terminal event.

The physical examination of the heart also provided significant presumptive evidence in favor of tricuspid insufficiency. Although the systolic murmur superficially stimulated mitral insufficiency it was heard best at the lower left sternal border and over the xiphoid process; it unmistakably faded at the apex and at the axillary area. Furthermore, the intensity of this

murmur diminished as clinical improvement was established. Indeed, in one patient the murmur could hardly be heard after right ventricular compensation had been restored.

Some of the evidence in the physical examination of the heart, however, did not suggest the diagnosis of tricuspid insufficiency. For example, a forceful apical impulse was observed in all but one patient. Ordinarily this finding is attributed to an enlarged left ventricle and therefore is common in mitral insufficiency. In the patients herein described the pronounced apical systolic thrust apparently was produced by the clockwise rotation of the right ventricle as it increased in size.

The murmur of tricuspid insufficiency has been said to increase in intensity after a deep inspiration [*3*] but this finding could not be verified in every case. This method of differentiating mitral from tricuspid insufficiency is probably only helpful in cases of slight to moderate degrees of tricuspid valve leak. In patients with advanced tricuspid regurgitation, increases in right ventricular filling do not occur with this maneuver and most likely alterations in intensity of the systolic murmur cannot be appreciated.

Although peripheral venous congestion and prominent systolic waves in the great veins initially suggested the diagnosis of tricuspid insufficiency, it must be acknowledged that these signs were not necessarily indicative of that lesion alone. They may be observed whenever, regardless of cause, right ventricular failure occurs and initiates an elevation in right atrial pressure. It is apparent, therefore, that these findings cannot be accepted as an absolute means of resolving the problem in the differential diagnosis between tricuspid and mitral insufficiency.

Considerable information was obtained from the conventional cardiac roentgenograms. The left atrial and right ventricular enlargement which were visualized were entirely consistent with the basic anatomic lesion, namely, mitral stenosis. In no instance, however, was the left atrial size greater than grade 3. (Table IV.) This is unusual with advanced, dynamically significant mitral insufficiency. At the same time it is clear that the x-ray examinations did not offer definite evidence of tricuspid insufficiency by revealing enlargement of the right atrium.

The catheterization studies clearly substantiated the inter-relationship between tricuspid insufficiency and mitral stenosis. This has been well documented in the past [*4*]. In each of the patients studied the stenosis was of marked degree, sufficient to initiate abnormal pulmonary vascular dynamics which in turn produced right ventricular hypertrophy and dilatation, and subsequent enlargement of the tricuspid ring and incompetence of the valve leaflets. The incidence of these related developments has been determined recently by exploring the tricuspid valve at the time of mitral commissurotomy. This can be accomplished if the mitral valve is approached through the right thorax [*5*]. A significant regurgitant jet at the tricuspid orifice was discovered in 15 per cent of 500 patients in whom this technic was used at operation [*6*].

FIG. 7. Left cardiac ventriculography. Direct injection of 40 cc. of 70 per cent diodrast into the left ventricle in this patient with mitral stenosis and tricuspid regurgitation failed to demonstrate any opacification of the left atrium. This eliminated the diagnosis of mitral regurgitation. Note opacification of aorta and the coronary vessels.

It is apparent that the most direct way of establishing the diagnosis of tricuspid insufficiency, under the circumstances described, involves opacification of the right or left ventricular chamber by ventriculography [*2*]. The rapid injection of diodrast into the left ventricle in these patients fails to demonstrate regurgitation across the mitral valve and opacification of the left atrium. (Fig. 7.) The injection of dye into the right ventricle, however, reveals regurgitation into the right atrium. (Figs. 4, 5 and 6.) Opacification of the atrium does not occur in patients with normal valves.

It is quite apparent that mitral commissurotomy is clearly indicated in patients, who, like those herein reported, have advanced stenosis

complicated by tricuspid insufficiency. Contrariwise, the operation may be considered contraindicated when the obstruction at the mitral valve is associated with marked mitral insufficiency. Accordingly, the ability to recognize patients with these lesions becomes a matter of concern. The total present clinical experience suggests that the correct diagnosis depends upon a careful evaluation of subjective and objective manifestations, aided by judicious application of a new technical advance, namely, ventriculography.

CONCLUSIONS

1. The clinical features of five patients with pure mitral stenosis and tricuspid regurgitation masquerading as mitral regurgitation are presented.

2. In each, a harsh systolic murmur was audible over the apex and along the left sternal border, with diminished intensity at the axilla and base. It was associated with the characteristic auscultatory events of mitral stenosis.

3. The electrocardiogram and x-ray provided evidence of right ventricular hypertrophy while catheterization of the left side of the heart demonstrated a ventricular filling pressure gradient across the mitral valve ranging from 12 to 24 mm. Hg.

4. In patients with this syndrome, injection of contrast material into the right ventricle leads to immediate opacification of the right atrium and confirms the presence of tricuspid regurgitation. Injection of contrast material into the left ventricle is not associated with any opacification of the left atrium.

5. Proper identification of this syndrome is important in view of the good results that are associated with mitral commissurotomy.

Acknowledgment: All the catheterization and other physiological data were supplied by the Brith Sholom Cardiopulmonary Laboratory, Hahnemann Medical College and Hospital of Philadelphia, Pennsylvania.

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The Fate of Human Aortic Grafts*

Autopsy Findings in Two Patients with Functioning Homografts for Eleven and Thirty-two Months

GRAHAM KNOX, M.D. *and* CHARLES F. BEGG, M.D.

ARTERIAL homografts have been extensively employed as a form of replacement therapy. The ultimate fate of these transplants is now assuming increasing importance. Because present knowledge is limited, it seemed desirable to report our findings in two patients in whom homologous aortic bifurcation grafts became available for study eleven and thirty-two months subsequent to successful implantation.

CASE REPORTS

CASE I. H. C. (108 848). This eighty year old man had an excision of an abdominal aortic aneurysm on November 15, 1954. A bifurcation homograft was inserted successfully. The graft employed had been obtained from a thirty-seven year old donor on September 27, 1954. It had been taken under unsterile conditions, and had been immediately frozen at −70°C. It had been sterilized on November 12, 1954, with ethylene oxide, and had been refrozen prior to use three days later.

The patient died from metastatic adenocarcinoma of the pancreas eleven months following the grafting procedure. Examination of the homograft at necropsy revealed it to be patent, and easily separable from the adjacent tissue. The wall was firm, and still slightly elastic whereas the wall of the host vessel was brittle and inelastic. The graft wall measured one to two times thicker than the host aorta. The intima of the patient's vessel was roughened by atheromatous plaques, many of which contained abundant calcific deposits. By contrast, the intima of the graft appeared smooth and intact throughout, with no apparent atheromatous or calcific changes. (Figs. 1 and 2.)

Microscopic examination revealed no true endothelial surface in the graft. The lumen was lined by a thin layer of hyaline fibrin-like material with an accumulation of dense protein precipitate beneath it. Subjacent to the former was a firm fibrous layer of tissue varying in width up to almost 1 mm. Some viable fibrocyte nuclei appeared in this layer. The media was composed of mummified, anuclear muscle cells, but the elastic fibers between them appeared unusually prominent, and thicker than normal. (Fig. 3.) The adventitia was dense and fibrous, and in many places it comprised more than half the thickness of the graft wall. Intimal thickening was most prominent at the anastomoses where cellular fibrous tissue was present.

CASE II. R. U. (116 525). This fifty year old, Puerto Rican woman had an excision of an abdominal aortic aneurysm on May 10, 1954, with continuity successfully established with a bifurcation homograft. The latter had been obtained on April 10, 1954, from a twenty-two-year old donor dying of chronic glomerulonephritis. The graft had been removed with sterile technic ten hours after death, and had been stored at 4°C. in a balanced salt solution containing 10 per cent homologous serum to which penicillin and streptomycin had been added. Just before use the storage medium had been cultured and was found to be sterile.

The patient died of an unrelated pulmonary embolus on January 7, 1957, thirty-two months after implantation of the graft. At autopsy the homograft was found to be slightly arched forward into the abdominal cavity with a loop of jejunum lying beneath it. (Fig. 4.) The graft wall appeared twice the thickness of the host vessel. Its lumen was patent and the intima appeared opaque and thickened. Only one small raised yellow plaque was present in the graft. The host aorta had a smooth intima throughout. (Fig. 5.) Microscopic studies of the homograft showed it to be similar to the specimen described in the first patient except that the elastic fibers were more prominent, and stained more intensely with special stains. (Fig. 6.)

COMMENTS

Creech et al. [*1*], DeBakey et al. [*2*] and Lord [*3*] have reported gross and microscopic findings in functioning aortic transplants surviving in human subjects for periods of 1 to 1,034 days.

Despite the well documented findings in canine experiments of accelerated degenerative changes appearing in homologous aortic grafts

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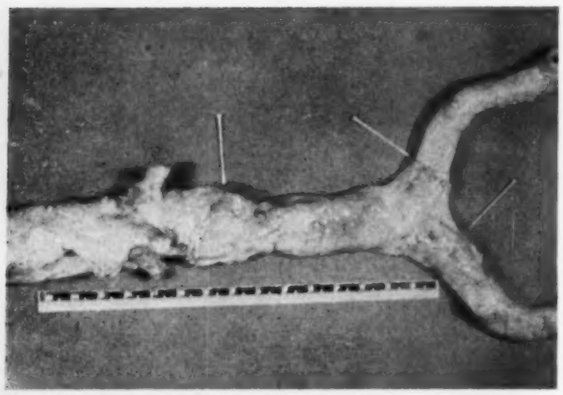

FIG. 1. Case I. The junction of the homograft with the patient's vessels is indicated by the pins. The renal arteries are seen proximal to the upper junction. Note fibrous coating of graft, eleven months following insertion.

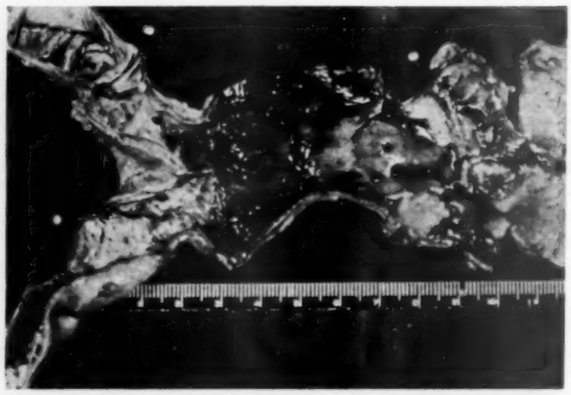

FIG. 2. Case I. Homograft and adjacent vessel opened. The intima of the graft is less roughened than the intima of the patient's aorta or iliac arteries.

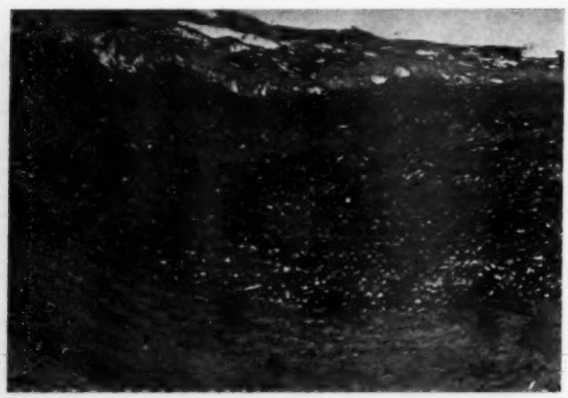

FIG. 3. Case I. An elastic tissue stain demonstrates preservation of the elastica. Above is the elastica interna. Finer fibrils lie between the muscle fibers. Aldehyde-fuchsin stain. Original magnification × 100.

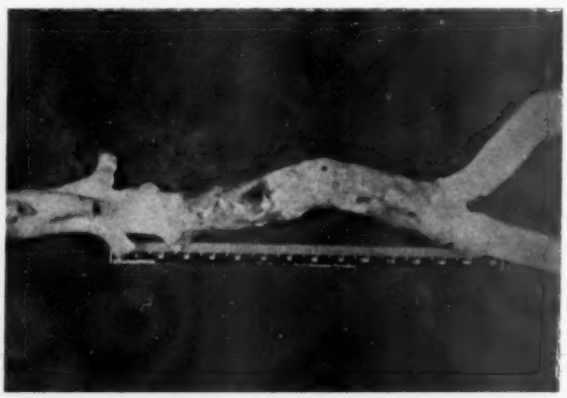

FIG. 4. Case II. Graft as it appeared thirty-two months following insertion. There is a smooth junction between the homograft and the patient's aorta and iliac arteries.

FIG. 5. Case II. Note the smooth intima of the homograft. Transverse wrinkles are present at the lower anastomoses.

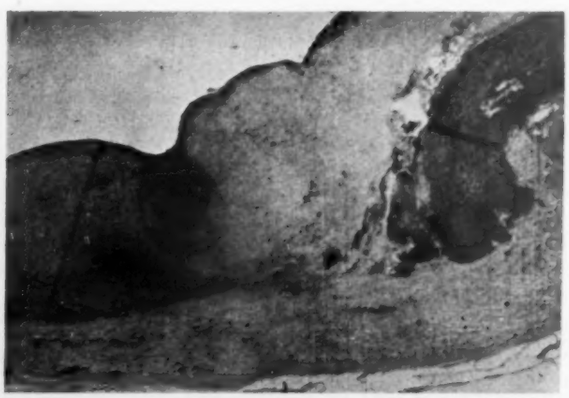

FIG. 6. Case II. Junction between host aorta and homograft. Media is replaced by fibrous tissue at suture line. On the right the elastic fibers of the media of the homograft stain more intensely than the elastic fiber in the host media on the left. Note fibrous thickening of intima of both graft and host vessel. Aldehyde-fuchsin stain.

within six months in animals rendered hypercholesterolemic [*4,5*], this phenomenon has not been apparent in the patients reported on to date. There is no ready explanation for this difference. It does not appear to be related to the method of graft preservation.

In both specimens reported herein no true endothelial layer remained in the graft but a modified fibrous-like layer had formed on the luminal surface which provided an efficient lining throughout the length of the graft. With the exception of the solitary plaque described in the graft in Case II no atheromatous change had developed in either specimen. Viable but avascular fibrous tissue had appeared in the subintimal layer suggesting that tissue at this level receives nutrition from the lumen of the vessel. Both grafts showed all muscle fibers to be mummified, whereas the elastic tissue was more prominent and stained more deeply than normal. Although it cannot be proved that the elastic tissue was actually living, its appearance suggested that it had maintained its integrity and strength. Ashing of these specimens, and examination for mineral content, with indirect illumination, demonstrated the presence of considerable amounts of calcium in the elastic fibers. This probably indicates a degenerative process but not necessarily a process which might interfere with tensile strength. A further buttress was provided by the development of a thick, dense, fibrous adventitia.

We conclude from our experience with these two cases, and from the reports of others, that the homograft provides a durable substitute for the patient's own vessels and that the integrity of the elastic tissue is important in the interim during which new fibrous tissue forms around the graft and beneath its luminal surface, and perhaps for a considerable time thereafter. Our findings suggest that the integrity and strength of the elastica are important and worthy of further investigation. No conclusions regarding the effectiveness of sterilization procedures or their possible harmful effects on the graft tissues are justified other than the opinion that the two methods used in these cases were effective and did no excessive harm to the graft tissues.

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Reviews

Bagassosis

A Review, with Further Historical Data, Studies of Pulmonary Function, and Results of Adrenal Steroid Therapy

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BAGASSE is the fibrous material remaining after the sugar-containing juice has been expressed from sugar cane. The word was first applied in France to the refuse from olive oil mills. It subsequently came to mean anything worthless, even being used to "describe a disreputable woman" [*1*].

Formerly bagasse was either discarded or burned for fuel in Louisiana, and it is apparently still used for this purpose in some cane-producing areas [*2*]. However, this substance has long since belied its "worthless" designation and has become a vital component of various insulating and acoustic materials such as beaver board and celotex.® It is also used in the manufacture of paper, fertilizer, explosives, poultry feed and refractory brick.

Chemically, bagasse consists of approximately 4 per cent ash and 2 per cent protein, the large remaining portion being made up principally of cellulose and other complex plant carbohydrates. Silica is present in very small quantities, comprising about one-half of the ash content [*3,4*].

Bagassosis, or bagasse disease of the lungs, is a disorder resulting from the inhalation of bagasse dust. It is typically an acute pneumonitis or bronchiolitis which is often associated with roentgenographic features resembling miliary tuberculosis. Dyspnea is the most characteristic symptom, although cough, hemoptysis, fever, weakness and weight loss are often present. Complete recovery usually takes place after a few weeks or months. One of the most intriguing aspects of this disease is the fact that until very recently all of the reported cases resulted from bagasse produced in Louisiana, which is shipped in bales to various parts of the world. There is also reason to believe that most if not all of these cases resulted from contact with bagasse produced at two sugar refineries near the small town of Raceland.

History. Bagasse was first used extensively in Louisiana for manufacturing purposes in 1922, when the Celotex plant near New Orleans began operation. It was not until nearly twenty years later that Jamison and Hopkins [*5*] reported the first case of bagassosis. From personal experience and conversation with older New Orleans practitioners it is known that this delay was not attributable to the sudden appearance of the disease *de novo*, but rather to failure to recognize and later to publicize instances of the disorder which had occurred in earlier years. In the comment that follows the presentation of Jamison's and Hopkins' [*5*] original report before the local medical society, it is pointed out that several cases had been observed previously, and a relationship between the respiratory illness and exposure to bagasse dust had already been established.

One of us (O. B. and his associate, Dr. Louis Monte) first recognized this association in 1937, after observing a typical case of the disease at Charity Hospital in New Orleans. This case of bagassosis is presented in some detail.

S. F. (No. L37-11474), a young white male laborer from Raceland, Louisiana, was admitted to the hospital on September 13, 1937, with the chief complaint of severe progressive dyspnea. The patient had con-

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sidered himself to be in good health until six weeks prior to admission when he experienced slight hemoptysis on two successive days, although he had no significant cough at that time. One week later he noted the abrupt onset of fever, chills, anorexia, weight loss, drenching night sweats and progressive dyspnea. Although he was able to continue his work for a short time, increasing dyspnea soon brought total incapacitation and the patient sought hospitalization.

Physical examination disclosed an acutely ill, dyspneic, cyanotic adult male who had obviously lost a considerable amount of weight. The temperature was 101°F., pulse 100/minute, respiration 40/minute. Expansion of the chest was symmetrical, but respiratory excursions were diminished. Accessory muscles of respiration were utilized. Scattered crepitant and subcrepitant rales were audible over the entire chest but were most prominent over the lower lung fields.

Laboratory studies were not remarkable except for a leukocytosis of 20,600 per cu. mm. with a moderate number of immature neutrophils. Sputum examinations for tubercle bacilli were negative. A roentgenogram of the chest taken at the time of admission was interpreted as showing an infiltration typical of advanced miliary tuberculosis throughout both lung fields. In addition, there was a suggestion of cavitation in the right lung. A chest film taken one month later revealed no change in the pulmonary disease, but cardiac enlargement was noted. Another film taken on November 23, 1937, disclosed moderate clearing of the lesions in the left lung and marked resolution in the right lung. The heart size had returned to normal.

In spite of the fact that sputum examinations failed to detect the presence of tubercle bacilli, it appeared to be obvious that the patient was suffering from miliary tuberculosis. During the first two weeks of hospitalization his dyspnea, cyanosis and general condition failed to improve and he exhibited an intermittent fever with temperature elevations to 102°F. Since no specific treatment existed for tuberculosis at that time, therapy consisted of bedrest, the administration of oxygen, and general supportive measures. On October 1, 1937, the patient was transferred to the tuberculosis unit where conservative management was continued.

In contrast to the expected course of events which would finally terminate in the patient's death, it was noted with astonishment that he slowly improved. By the sixth week of hospitalization his respiratory rate had returned to normal and his fever had abated. Soon thereafter he became entirely asymptomatic and was discharged from the hospital with the diagnosis of "pneumoconiosis" after three months of treatment. He has been seen in subsequent years and still enjoys good health.

The course of the patient's illness prompted an investigation into his occupational history and it was then learned that he was employed in a sugar refinery in Raceland, Louisiana, where he had been exposed to heavy concentrations of bagasse dust. By the time of his admission to the hospital similar symptoms had already developed in three fellow workers in the plant and two more workers subsequently contracted the same illness. These observations led to the conclusion that exposure to bagasse dust may have caused the disease. Conversation with other physicians at this time revealed that similar cases had been observed sporadically even before our own, but the relationship to bagasse had not been recognized.

A visit to the employing sugar refinery disclosed many milder cases of the disease among the laborers. Even the plant superintendent suffered from a moderate cough and mild dyspnea. The superintendent's chest x-ray showed shadows similar to, but less pronounced than, those of the index case. Plans to investigate fully this occupational hazard were formulated but unfortunately could not be carried out because of administrative difficulties.

In the next few years several more cases of bagassosis were observed, both in private practice and at Charity Hospital. It was noted with interest that all of the patients were employees of the same plant. Another refinery, located less than twenty-five miles away, owned by the same company and operated under nearly identical conditions with regard to the bagasse, was apparently not plagued with bagassosis. This has remained true in our subsequent experience, and is still unexplained.

Three of these early cases were reported in 1939 before a staff meeting at Mercy Hospital in New Orleans under the title of "Occupational Lung Disease" but unfortunately a planned publication was never completed.

Jamison and Hopkins [*5*] in 1941 were the first to publish a case of bagassosis. They originally attributed the disease to an unidentified fungus believed to have been present in the bagasse dust and accordingly suggested the name "bagasscosis." In 1942 Castleden and Hamilton-Paterson [*6*] observed four cases in England, where the disease occurred in workers breaking imported bales of Louisiana bagasse in a dry atmosphere. These authors initially used the term "bagassosis" and this has remained the most popular designation for the disorder. The sudden appearance of the disease in England was apparently due to a change in the method of processing the bagasse. Before 1940 the bales were broken under water. With the advent of World War II the bales of bagasse were packed more firmly to conserve shipping space, and consequently could not be processed by the wet method. The new procedure required that the

bales first be broken with a pickaxe and then fed into a machine known as a shredder which further ground the material by a dry, dusty process.

Sodeman and Pullen [7] (1943), preferring the designation "bagasse disease of the lung," were the first to describe the pathological features of the disorder after studying two needle biopsies of the lung in one patient and autopsy sections from another. Along with his co-workers Sodeman has also contributed extensively to the etiologic and clinical aspects of the disease, adding fifteen cases to the literature [*8–10*].

Hunter and Perry [*4*] (1946) studied most of the men who were exposed to bagasse dust in the English plant from which Castleden's and Hamilton-Paterson's index English cases were reported. They showed that in ten of twenty-one workers who were exposed to the dust symptoms of bagassosis developed. They also pointed out that the disease is fundamentally an acute bronchiolitis.

Lemone et al. [*11*] (1947) have emphasized the roentgenologic features of bagassosis in firebrick workers in Missouri. The conditions of exposure were similar to the English cases, and again the bagasse was imported from Louisiana.

The report of McDaniel and Hull [*12*] in 1952 is the only one from the United States in the past five years. Their two patients were observed in Houston, Texas. Exposure occurred in a building-material plant which was using Louisiana bagasse [*13*].

Ganguly and Pal [*14*] (1955) and Singh [*15*] (1955) have described the disease in India, where bagasse is used as a raw material in the manufacture of paper and "press board" [*16*]. Although there is a possibility that some of Singh's cases may have suffered from illnesses other than bagassosis, there can no longer be doubt that the disease has resulted from contact with bagasse produced from cane grown in India [*16*].

From these reports it is now clear that bagassosis is not restricted to contact with Louisiana-grown cane, as we once believed, but must indeed be a hazard whatever the source of the bagasse. Manas [*17*] (1945) in Cuba and Boccia [*18*] (1951) in Argentina have called attention to the possible appearance of bagassosis in their countries since sugar cane is grown extensively there and contact with waste bagasse is common. Nonetheless, neither of these authors has observed a single instance of the disease. Why no cases have been reported from Puerto Rico, Cuba, Argentina, the Philippines, Hawaii and other sugar cane-producing areas remains something of an enigma, especially since bagasse is now used for manufacturing purposes in some of these countries.

Clearkin [*19*], writing from British Guinea, noted that a "considerable number of patients suffering from respiratory disorders, especially asthma," had worked in cane or rice mills in the Caribbean area. He related these illnesses to exposure to "megass" (or bagasse) dust during the cane-grinding season, or to padi dust, but he described no definite case of bagassosis. Since his patients gave positive skin tests to extracts of megass or padi dust, obtained relief and sometimes cure by avoiding the offending agent, and also responded to desensitization with appropriate extracts, he concluded that these disorders were the result of an allergic reaction. Whether or not any of these patients actually had bagassosis remains uncertain, but it seems doubtful to us since they were apparently in contact with fresh sugar cane rather than dried bagasse. It is also odd that no documented case of bagassosis has ever been reported from this area.

In all, only an approximate fifty-three cases of bagassosis have been reported in the world literature. However, our own experience suggests that this disease has been by no means as rare as the number of reported cases would seem to indicate. One of us (O. B.) has personally observed some twenty cases since 1937 and, as previously indicated, symptoms suggestive of the disorder have been detected in a number of bagasse workers who never sought medical attention. In addition, it can hardly be doubted that a great many other cases have come under medical observation and escaped correct diagnosis. In spite of preventive measures which have been introduced in the process of handling bagasse, sporadic cases continue to appear. We have seen three such cases since 1954 at the Veterans Administration Hospital, New Orleans, Louisiana, and present detailed descriptions of these patients in this report. Two of these patients are the first to be studied by evaluation of pulmonary function and are also the first to be treated with adrenal steroids.

CASE 1. H. O., a twenty-one year old white male laborer from the vicinity of Raceland, Louisiana, was admitted to the hospital on November 13, 1954,

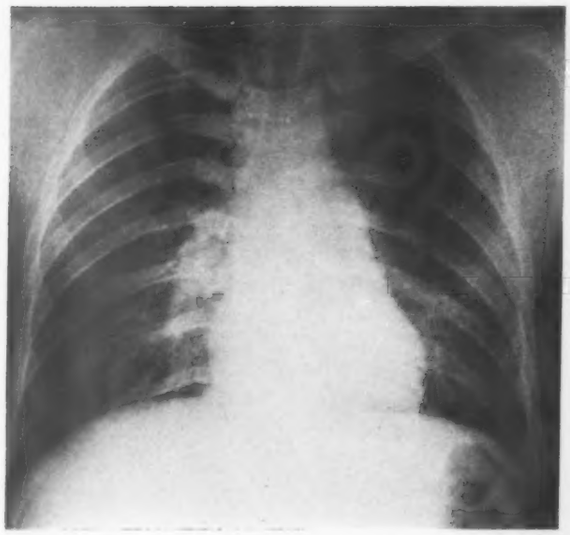

FIG. 1A. Case 1. Admission roentgenogram of the chest showing fine miliary densities throughout both lung fields. The lesions are most prominent in the medial and lower portions of the lungs.

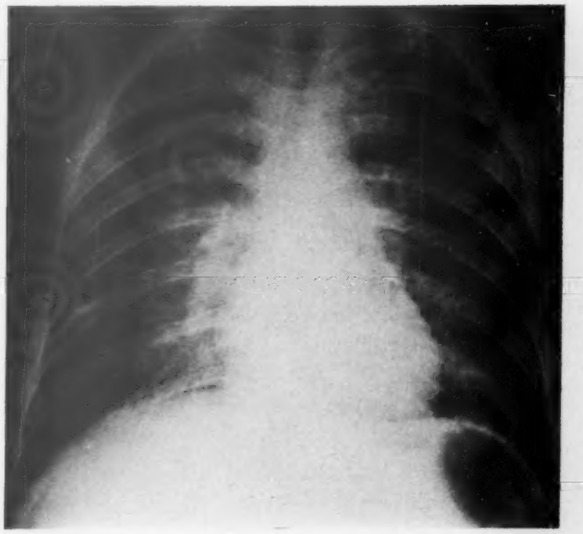

FIG. 1B. Case 1. Roentgenogram of the chest taken two days after admission showing marked progression of the pulmonary lesions. (Note the striking similarity to miliary tuberculosis.) At this point the patient's symptoms were rapidly increasing in severity.

complaining of increasing dyspnea. During the previous three months he had been employed in a mill which manufactured paper from raw bagasse. He did not work with the bagasse directly, but was frequently in close contact with the material when it was being unloaded and brought into the plant. Five days prior to admission a cough developed productive of thick, mucoid sputum which was frequently streaked with blood. Headaches, sore throat, fever, chilly sensations and weakness soon appeared. Two days before hospitalization he noted dyspnea on exertion, and this symptom rapidly increased in severity. After viewing the patient's chest x-ray, a physician referred him to the hospital with a presumptive diagnosis of miliary tuberculosis.

Physical examination on admission disclosed an asthenic young man in acute respiratory distress. His temperature was 103.2°F., pulse 120 per minute, respiration 40 per minute, and blood pressure 102/62 mm. Hg. The pharynx was slightly injected. The chest was symmetrical, and equal expansion was present bilaterally. Diffuse moist inspiratory rales were audible throughout both lung fields. The liver and spleen were not enlarged. No clubbing was present, but there was slight cyanosis of the nail beds.

A roentgenogram of the chest (Fig. 1A) disclosed many miliary densities throughout both lung fields. These lesions appeared as tiny discrete nodules which were most conspicuous and confluent in the hilar areas. There was slight prominence of the pulmonary artery segment.

Blood leukocytes were 25,400 per cu. mm., polymorphonuclear neutrophils 73 per cent, and eosinophils 1 per cent. The hematocrit was 46 per cent, red blood cells 5,000,000 per cu. mm., hemoglobin 15.5 gm. per 100 cc., and sedimentation rate 31 mm. (Wintrobe). Urinalysis was normal except for a trace of albumin. Multiple smears and cultures of the sputum failed to detect the presence of pathogenic bacteria, tubercle bacilli or fungi. Virus cultures, carried out in the chick embryo, yielded negative results. Blood agglutinations, including cold agglutinins and those for tularemia, were also negative. The serum bicarbonate level was 31.3 mEq. per L.; other blood chemical determinations were within normal limits. An examination of the cerebrospinal fluid detected no abnormalities. Intradermal tests for tuberculosis produced no reaction with first and second strengths of the purified protein derivative. The histoplasmin and coccidioidin skin tests were likewise negative. An initial electrocardiogram was suggestive of right ventricular strain, but subsequent tracings were normal.

The patient exhibited slight initial improvement after the administration of oxygen and penicillin, but during the next few days his condition became critical. Dyspnea increased alarmingly. His respiratory rate rose to 70, the temperature ranged up to 104°F., and a tachycardia of 140 was noted. Cyanosis increased in spite of continuous oxygen and intermittent positive pressure breathing. Repeat chest films on November 15 and November 16, 1954 (Figs. 1B and C) disclosed marked progression of the pulmonary lesions.

Because of the possibility that the patient might be suffering from miliary tuberculosis, administration of streptomycin, para-aminosalicylic acid (PAS) and isoniazid (INH) was begun (November 15, 1954). Terramycin® and gantrisin® were also administered. Progressive anoxia and the patient's rapidly

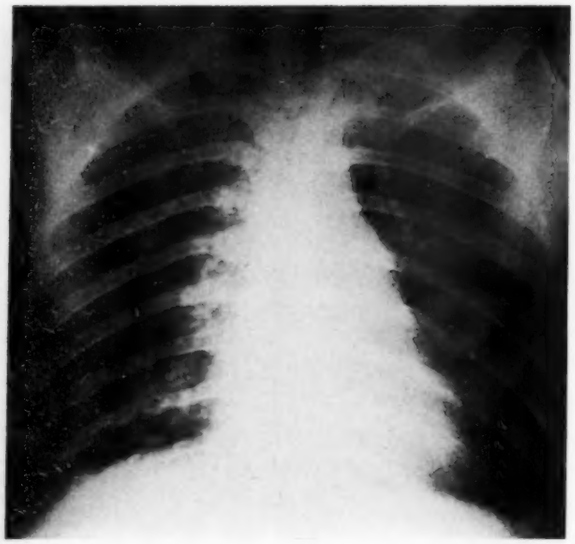

FIG. 1C. Case I. Portable anterior posterior roentgenogram of the chest taken on third day following admission showing still further extension of the disease process. The patient's clinical condition continued to deteriorate and he appeared critically ill.

FIG. 1D. Case I. Chest x-ray taken one month after admission. Marked improvement has taken place following treatment with ACTH and cortisone. The patient was almost asymptomatic and appeared clinically well.

deteriorating clinical condition precipitated the introduction of adrenal steroid therapy on November 16, 1954, as a potential lifesaving measure. Cortisone 300 mg., and ACTH 15 units, were given on this date. Immediate and dramatic clinical improvement resulted. By the following day the patient was fever-free. His pulse rate fell to 90, his respiratory rate decreased to 30, and his cough, dyspnea and cyanosis diminished. On this date 200 mg. of cortisone was given and on the next day the patient received 20 units of ACTH. Thereafter no further steroid therapy was employed. On November 18, 1954, PAS, INH, penicillin and terramycin were discontinued. Chloromycetin® was started and administered along with streptomycin and gantrisin for one month. The patient continued to improve. By the end of the third week cyanosis and dyspnea had disappeared and by the end of six weeks his cough had subsided and he was completely asymptomatic.

Serial chest films disclosed minimal resolution at two weeks, marked improvement at four weeks (Fig. 1D), and complete clearing at four months. The patient was discharged from the hospital on December 30, 1954. He has been seen as recently as March, 1957 and remains perfectly well.

Comment: This case illustrates bagassosis in its severest and most rapidly progressive form, even though exposure to the offending agent was apparently quite mild. There is little doubt that the patient's illness had reached life-threatening proportions at the time of introduction of steroid therapy. Although the fulminating course of the disease precipitated "panic" therapy in the form of multiple antibiotics and antituberculous drugs, the dramatic clinical improvement which followed the administration of adrenal steroids clearly suggests these agents as the ones responsible for the patient's recovery.

The problem of differential diagnosis is also demonstrated by this case since miliary tuberculosis, bronchiolitis of bacterial or viral origin, and the Hamman-Rich syndrome were all given serious consideration before the true nature of the patient's illness was accepted.

CASE II. W. R., a thirty year old Negro male laborer, was referred to the hospital on October 3, 1955, with a diagnosis of probable pulmonary tuberculosis. History disclosed that he began employment in a sugar refinery near Raceland, Louisiana, in February, 1955. He was assigned to a section where bagasse was ground into smaller fragments. Because of the exposure hazards in this area, protective face masks were worn but the patient used this device only intermittently. At the end of six weeks he began to complain of a non-productive cough and mild exertional dyspnea. A chest film taken by his physician was allegedly normal and he was treated symptomatically. He recovered quickly and on returning to work his job was changed to loading sugar, but he still worked in the general vicinity of the dry bagasse. He had no further difficulty until June, 1955, when there again developed a severe cough which on this occasion was productive of small amounts of yellow sputum. He also complained of fever and moderate dyspnea. On the advice of his physician the patient

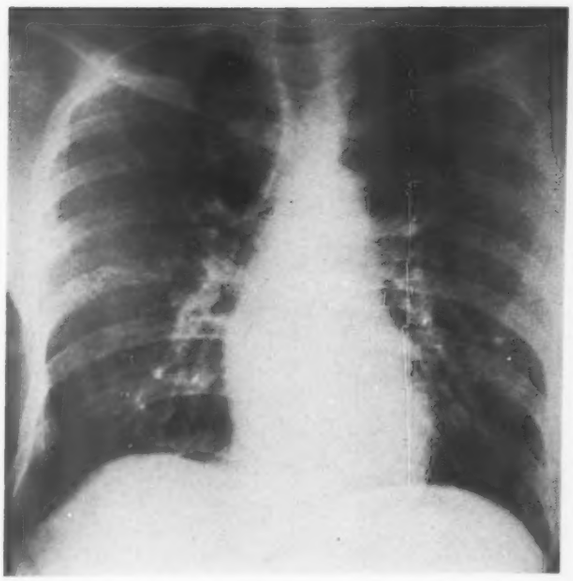

FIG. 2A. Case II. Roentgenogram of the chest showing extensive fine miliary densities symmetrically distributed throughout the major portions of both lungs. Only the extreme apices appear to be spared. Again the similarity to miliary tuberculosis is very pronounced.

FIG. 2B. Case II. Chest film taken three months after admission showing complete clearing of the pulmonary lesions.

discontinued work for one week and was treated symptomatically. Again recovery appeared to be complete, but on returning to work he became aware of slightly reduced exercise tolerance.

Nonetheless, he did well until one month prior to admission when there again occurred a cough productive of small amounts of yellow sputum. The cough became progressively more severe and the patient also complained of dyspnea, chilly sensations, fever, anorexia and weight loss of ten pounds. A second chest film demonstrated many tiny miliary densities in both lungs and the patient was told that he had "pneumonia." Daily injections of penicillin were given for one week, during which time he experienced considerable symptomatic improvement but continued to complain of a harassing cough and exertional dyspnea. On September 27, 1955, a direct smear of the sputum was reported to be positive for acid-fast bacilli. The patient was then told that he had "tuberculosis" and was referred to the hospital for further observation and therapy.

Physical examination on admission disclosed a muscular, well-nourished, young Negro man, who did not appear to be ill. The temperature was 98.6°F.; pulse 82, and blood pressure 125/75 mm. Hg. No abnormalities could be detected other than slightly diminished respiratory expansion of the chest and accentuation of the pulmonic second heart sound.

Roentgenograms of the chest revealed extensive, fine, stippled and linear densities throughout the major portions of both lungs with some sparing of the apices. (Fig. 2A.) Laboratory determinations were as follows: red blood cells 5,750,000 per cu. mm., hemoglobin 16.4 gm., hematocrit 52 per cent, white blood cells 7,100 per cu. mm., neutrophils, 63 per cent, lymphocytes 33 per cent, eosinophils 1 per cent, and sedimentation rate 19 mm./hr. The serum bicarbonate level was 28.6 mEq. per L. Other blood chemical determinations, serological determinations and urinalysis were normal. Multiple sputum examinations and cultures of gastric content were negative for tubercle bacilli. Tuberculin skin tests were negative in both first and second strength. Skin testing with histoplasmin and coccidioidin produced no reaction. An electrocardiogram was normal. Studies of pulmonary ventilatory function and arterial blood gases were abnormal, as indicated in Tables I and II, and are discussed later.

Shortly after admission the patient's cough and dyspnea subsided. Thereafter he remained entirely asymptomatic and gained twelve pounds in weight during the period of hospitalization. No form of therapy was utilized other than a program of modified bedrest. Follow-up chest films revealed moderate resolution of the pulmonary lesions after a period of two weeks and complete clearing in three months. (Fig. 2B.) The patient was discharged on December 3, 1955. He has since changed his occupation and has had no further respiratory illnesses.

Comment: This case illustrates a milder form of bagassosis which is self-limited and which requires no specific therapy if the patient is simply removed from contact with the causative agent. It is interesting to note that each re-exposure produced symptoms of increasing severity and it seems highly likely that a grave illness similar to

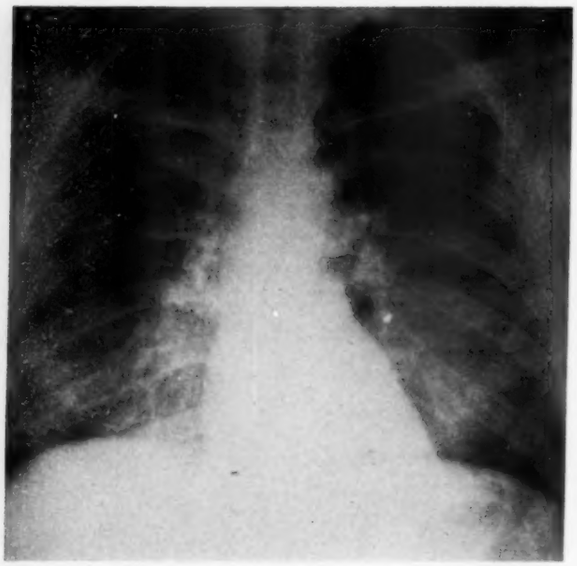

FIG. 3A. Case III. Admission x-ray of the chest demonstrating a vague generalized hazy appearance together with poorly defined patchy and linear densities throughout the major portions of both lungs. The lesions are symmetrical and most pronounced in the cardiophrenic areas. Again the apices are spared.

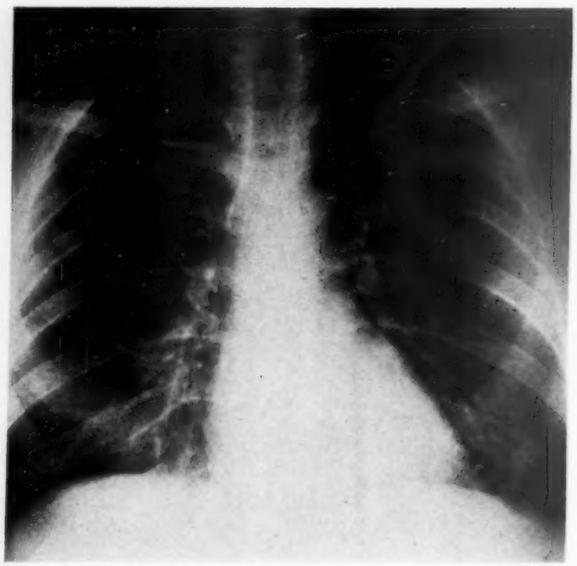

FIG. 3B. Case III. Roentgenogram of the chest less than three weeks after admission, demonstrating the marked clearing of the pulmonary lesions which followed therapy with prednisone.

that observed in H. O. (Case I) would have occurred if the patient had been allowed to return to his original occupation for a third time. The difficulties involved in differentiating this disease from miliary tuberculosis are again pointed out by this case. The clinical picture and roentgenographic findings were certainly compatible with miliary tuberculosis and this diagnosis appeared to be further supported by the alleged demonstration of acid-fast bacilli in the patient's sputum. We suspect, however, that this finding represented either a laboratory error or, if acid-fast bacilli were actually present, they were organisms other than Mycobacterium tuberculosis. This conclusion appears to be borne out by the negative tuberculin skin tests, negative bacteriological findings during the course of hospitalization, and the benign clinical course which terminated in complete recovery.

CASE III. R. F., a twenty-eight year old white male factory worker, was admitted to the hospital on April 16, 1956, complaining of progressive dyspnea of about two months' duration. For the past seven years he had been employed in a plant which manufactured wall board from bagasse. He operated a machine which cooked wet bagasse under steam pressure. His only contact with dry bagasse dust was for brief periods while eating lunch. Except for an alleged gradual unexplained weight loss of 44 pounds during the six months preceding admission, the patient had considered himself well until mid-February, 1956, when there developed grippe-like symptoms consisting of malaise, fever and arthralgia. He did not feel ill enough to stop work and within two days he had apparently recovered. However, several days later he experienced the insidious onset of a dry cough. His cough gradually increased in severity and soon became productive of small amounts of thick, malodorous, yellow sputum. The sputum was occasionally "rust" colored but no frank hemoptysis was noted. Shortly after the appearance of cough the patient also began to complain of exertional dyspnea which gradually became so severe that he was unable to walk more than a few yards.

Physical examination on admission disclosed a well-developed, well-nourished young man who was slightly dyspneic at rest. Vital signs were normal except for a respiratory rate of 35 per minute. A paroxysmal, dry cough was precipitated by deep breathing. The chest was symmetrical, and resonance was normal. Many fine, crackling inspiratory rales were audible over both lung bases posteriorly. No cyanosis or clubbing was observed.

Roentgenograms of the chest (Fig. 3A) revealed poorly defined patchy and linear densities radiating outward from the hilar areas into both lung fields, with greatest prominence at the bases. A diffuse haze was also apparent overlying both lungs, but no miliary lesions could be detected.

Laboratory studies revealed blood leukocytes 9,300 per cu. mm. with a normal differential count. Red blood cell count was 6,040,000 per cu. mm., hemoglobin 19.7 gm. per 100 cc., hematocrit 53 per cent. Urinalysis and blood chemical findings

TABLE I

PULMONARY VENTILATORY FUNCTION IN TWO PATIENTS WITH BAGASSOSIS

Data	Case II				Case III			
	10/6/55	11/30/55	6/5/57	Predicted	4/19/56	6/18/56	3/14/57	Predicted
Vital capacity (ml.)	2,114	3,000	4,479	4,252	3,437	4,650	4,818	4,125
One-second vital capacity (%)	.....	69	91	83	72	77	78	83
Three-second vital capacity (%)	.....	96	100	97	93	92	97	97
Minute ventilation (L./min.)	9.3	8.8	12.0	6–12	13.7	12.9	11.7	6–12
Oxygen uptake (ml./min.)	290	290	483	.....	302	435	309	.....
Ventilatory equivalent L./100 cc.	3.2	3.0	2.5	1.5–4	4.6	2.9	2.5	1.5–4
Maximum breathing capacity (L./min.)	97	99.5	165	143	78.3	110.4	122	153

TABLE II

ARTERIAL BLOOD GAS STUDIES IN TWO PATIENTS WITH BAGASSOSIS

Data	Case II		Case III		Mean Normal
	11/30/55	6/5/57	4/26/56	3/14/57	
O_2 saturation, breathing room air (%)	91.0	96.2	90.8	96.2	97 ± 1.0
O_2 saturation, breathing 100 per cent O_2 (%)	100.0	100.0	100.0	100.0	100.0
CO_2 tension (mm. Hg)	42.0	41.0	42.0	41.0	41.0
pH	7.4	7.37	7.36	7.4	7.4

were within normal limits. Sputum examinations for tubercle bacilli and fungi revealed no abnormalities. Intradermal skin tests for tuberclosis, histoplasmosis and coccidioidomycosis produced no reactions. The electrocardiogram was normal. Studies of pulmonary ventilatory function and arterial blood gases were abnormal, as indicated in Tables I and II and discussed later.

Following admission to the hospital the patient remained afebrile but he continued to complain of dyspnea and cough, and slight cyanosis developed. On May 2, 1956, prednisone therapy was initiated in doses of 30 mg. daily. The patient exhibited almost immediate clinical improvement and within ten days appeared to be clinically well; however, very slight exertional dyspnea and a mild cough persisted for about six weeks. Prednisone was reduced to 20 mg. daily on May 10, 1956, and was discontinued on June 22, 1956. Serial roentgenograms of the chest disclosed no significant change prior to the institution of steroid therapy but four days later marked improvement had taken place. (Fig. 3B.) The patient was discharged on July 7, 1956, and returned to his former occupation. He has had no further significant difficulty but when last seen on March 14, 1957, he again complained of a mild, chronic cough productive of small amounts of mucoid sputum. An x-ray of the chest revealed no abnormalities at that time.

Comment: This case represents a variation of the roentgenographic changes which bagassosis may produce. The striking prominence of dyspnea in this illness is again pointed up. The benefits of steroid therapy are much more difficult to evaluate than in Case I, since spontaneous improvement is the rule in this disease. Nonetheless, the authors believe that these agents exerted a specific beneficial effect.

ETIOLOGY

In spite of the fact that bagassosis is unquestionably caused by the inhalation of bagasse dust, the specific physiopathological mechanism involved in the relationship has never been clearly defined. The disease has been variously attributed to a specific irritant property of the bagasse fiber itself, to its silica content, to allergy, to microorganisms present in the dust, and to all combinations of these factors.

Silica has been generally discarded as an

etiologic agent because the minute quantities of this substance found in bagasse are regarded as innocuous [*4,11,20*] and, in addition, the clinical picture of bagassosis in no way resembles that of silicosis.

An allergic state has been favored by many investigators, notably Castelden and Hamilton-Paterson [*6*], Ganguly and Pal [*14*], Singh [*15*] and Clearkin [*19*]. Bagassosis is, however, only very superficially similar to an allergic disorder and the usual stigmas of asthma or Loeffler's syndrome are absent. Although Castelden's and Hamilton-Paterson's [*6*] patients exhibited positive skin reactions to extracts of bagasse dust, Sodeman and Pullen [*8*] demonstrated that a non-specific irritant was responsible since both patients and control subjects reacted alike. Similarly, using intracutaneous tests Gerstl et al. [*21*] were unable to find evidence of an allergic factor in the experimental disease of rabbits. The fact that symptoms recur upon re-exposure of the patients to the offending agent, and the absence of illness in workers who are in contact with bagasse only after it has been processed by heat, has been pointed out as suggestive of an allergic mechanism. However, this is hardly acceptable evidence since heat would destroy not only the postulated allergenic proteins but also any micro-organisms that might be present in the dust.

It has been our impression, for many years, that bagasse fiber which has been stored outside and exposed to rain and the humid subtropical climate of southern Louisiana for long periods is much more likely to produce bagassosis than fresher fiber which has been stored indoors. This observation quite naturally led us to the conclusion that micro-organisms grew in the exposed fiber and were actually responsible for the disease. Since all cases of bagassosis prior to 1955 apparently resulted from contact with bagasse produced in Louisiana, we were further tempted to conclude that the organism (probably a previously unidentified fungus) was peculiar to this area. As has been indicated in the foregoing sections, at least a part of this theory collapsed with the reports of Singh [*15*] and Ganguly and Pal [*14*] from India. The possibility of a fungal etiology is not so easily dismissed. A myriad of bacteria and fungi have been isolated from bagasse. Hunter [*20*] found 240,000,000 fungal spores of twenty different species in one gm. of the dust. These included species of Aspergillus, Monilia, Penicillium, Trichoderma, Mucor and Rhizopus. On clinical grounds the close similarity between bagassosis and certain occupational pulmonary disorders which have been attributed to microorganisms and their products was appreciated soon after recognition of this disease. We refer specifically to "asthma due to grain rusts" (notably Puccinia graminis) described in farmers by Cadham [*22*] in 1924, to "Asthma due to a fungus, *Alternaria*" described by Hopkins et al. [*23*] in 1930, and to the respiratory illness of tie peelers and sawmill workers described by Towey et al. [*24*] in 1932. The latter disorder in particular bears an amazing similarity to bagassosis and is apparently caused by fungus spores (Coniosporium corticale) found in maple bark. The various pulmonary diseases of hay workers and threshers ascribed to species of Aspergillus, Penicillium and Mucor contained in mouldy hay or grain should also be included in this group [*25*]. Although not previously emphasized, other pulmonary mycoses, particularly histoplasmosis and coccidioidomycosis, might well be added to this list, since both of these diseases are apparently contracted by the inhalation of dust-borne fungi and are in many instances self-limited.

In addition to these comparisons, there is some experimental evidence in support of a fungus etiology of bagassosis. Gerstl et al. [*21,26*], working with animals, showed that intravenous and intratracheal administration of bagasse dust, as well as inhalation of this material, resulted in severe, often fatal, pneumonitis and bronchiolitis if the material had not been previously autoclaved or treated with formalin. Sterilized bagasse produced only mild granulomatous lesions which were not associated with clinical illness. The progressive disease and death of rabbits was attributed to microorganisms, especially Aspergillus, contained in the dust. Gerstl and his co-workers also concluded that the lesser lesions in animals exposed to sterilized material represented a foreign body reaction produced by the direct irritant properties of the fiber itself.

In spite of these findings, the evidence for a fungus etiology of bagassosis remains indirect and incomplete. Although Jamison and Hopkins [*5*] found an unidentified fungus in the sputum of their patient, and Monilia and Aspergillus have been cultured from occasional cases by others [*8,11,13,20*], all attempts to isolate a truly pathogenic fungus from patients with this disorder have been unsuccessful. The same

objection applies to a bacterial cause of the disease. Likewise, attempts to incriminate the endotoxin of Aerobacter cloacae, which may be present in bagasse as well as in cotton, have been inconclusive [*27*].

The strongest evidence in favor of a primary pathogenic role of the bagasse dust per se was obtained by Sodeman and Pullen [*7,8*] who demonstrated foreign particles, assumed to be bagasse fibers, in lung biopsy specimens of a patient with bagassosis. The foreign objects appeared to be embedded in the pulmonary tissue and were associated with a fibroblastic reaction. The findings led these authors to conclude that "a pneumonitis from dust is likely, and the examination of tissue obtained by lung puncture . . . . supports the view that bagasse particles mechanically, chemically, through one of its fractions or by introduction of an unknown infection, are responsible for the pathological picture" [*8*]. These authors apparently favored a direct toxic effect of the bagasse particles [*9*]. The mechanical factor is interesting since the clinical picture of an acute bronchiolitis characterized by severe cough and dyspnea might be readily attributed to blockage of the small airways by accumulations of bagasse dust, which swells under the influence of the bronchial secretions and results in small areas of atelectasis. When infection is superimposed, typical bronchiolitis and bronchopneumonia might result. At least this is the theory favored by Hunter [*20*]. Nonetheless, certain objections to this mechanism are again apparent. The actual identification of the foreign particles is based on indirect evidence and similar structures could not be demonstrated in the lungs of rabbits dying of the experimental disease. It has been suggested that the absence of bagasse fibers in the lungs of these animals might be due to the smaller size of their airways as compared to man; however, it also indicates that mechanical obstruction by foreign particles is not necessary for production of the disease.

From the foregoing discussion it becomes obvious that many factors may be involved in the etiology of bagassosis and at present none of the proposed mechanisms seem to satisfy all objections. Further studies are needed, with particular attention directed toward the role of microorganisms of ordinarily low virulence. Additional pathological information would, of course, be highly desirable and might help to clarify the puzzling etiology of this disease, but it seems likely that appropriate materials will be difficult to obtain.

PATHOLOGY

Few diseases are associated with a greater paucity of pathological studies than is bagassosis. Sodeman and Pullen [*7,8*] have contributed almost exclusively what little is known about this aspect of the disorder in man, and their experience was limited to two lung biopsies and one necropsy in two cases. In both instances needlelike spicules, some large and some small, the latter approximately 2 by 8 μ in size, were found in the pulmonary tissue. Since these particles rotated polarized light in a manner similar to bagasse fiber they were assumed to be identical. Tissue changes included an interstitial fibroblastic reaction and the presence of large cells with foamy cytoplasm in the alveolar spaces.

As previously indicated, Gerstl et al. [*21,26*] have provided a detailed description of bagassosis in rabbits after exposing the animals to conditions simulating those under which the human disease is acquired. "The complex morphology of the lesions found in these animals includes hemorrhagic pneumonia, bronchiolitis, with plugging of passageways by cellular exudate and debris, interstitial thickening by exudate and fibroblastic proliferation, as well as of foreign body reaction" [*26*]. The presence of "large foamy exudate cells and plugging of the bronchi were the features whereby the experimental most closely resembled the spontaneous disease" [*26*].

The question as to whether or not bagassosis may result in chronic pulmonary disease remains uncertain. Hunter and Perry [*4*] reported two patients in whom exposure was less intense but more prolonged than in their other acute cases. In one of these patients respiratory insufficiency developed and he died within four years. His autopsy, the only other postmortem examination referred to in the medical literature, disclosed extensive pulmonary fibrosis, emphysema and bronchiectasis. The other patient was asymptomatic but presented x-ray evidence of pulmonary fibrosis. The fate of this patient is unknown. No other reports have been found in which exposure to bagasse has led to progressive pulmonary fibrosis, although Ganguly and Pal [*14*] have postulated such an outcome. We have observed one patient with extensive progressive pulmonary fibrosis who had a history of prolonged occupational exposure to bagasse. However, it is impossible to

decide whether or not a causal relationship existed either in this case or in the patients previously cited.

CLINICAL FEATURES

The occupations which are associated with exposure to bagasse dust are those involving heavy manual labor. This accounts for the occurence of the disease almost exclusively in men twenty to forty-five years of age. Indeed, only Sodeman [*10*] found a woman suffering from this condition. No racial differences have been observed. Working conditions favorable to the contraction of the disease include a dusty atmosphere, usually in a poorly ventilated space, and almost invariable contact with dry bagasse.

A review of the reported cases of bagassosis immediately impresses one with the consistency of the clinical picture. In most instances, after exposure to the dust for periods of a few weeks to a few months, symptoms appear over a space of several days. Cough, exertional dyspnea and slight fever are usually the initial complaints. Black sputum with a bad taste resembling rotten bagasse has been observed by Gillison and Taylor [*28*] and others [*4,20*]; however, we have not encountered this phenomenon and in our experience the sputum is characteristically scanty and mucoid. Hemoptysis of a mild degree is rather common, but frank pulmonary hemorrhage is rare, if it occurs at all.

As the disease progresses, dyspnea usually dominates the clinical picture and soon becomes incapacitating. Cyanosis may appear in more severe cases. Weakness is often prominent and may be associated with anorexia and loss of weight. These latter symptoms sometimes antedate all others and the amount of weight lost is at times quite impressive.

Fever is usually slight to moderate, but temperature elevations as high as 104°F. are observed in the more severe cases. Other symptoms may include night sweats, chilly sensations and retrosternal pain. True chills are less common. Pleuritic pain is absent.

Physical examination may reveal little more than various degrees of dyspnea and possibly cyanosis. The pulse rate is elevated in proportion to the temperature. Diffuse or localized crepitant rales can usually be heard over the lung fields and the second pulmonic heart sound may be accentuated.

A slight or moderate blood leukocytosis is usually present, but eosinophilia is not observed. Sodeman and Pullen [*8*] have described a polycythemia in some of their patients, and our own patients have also exhibited this finding. The serum bicarbonate level may be significantly elevated, indicating the presence of respiratory acidosis. Electrocardiographic evidence of right ventricular strain is sometimes noted. This finding, together with accentuation of the pulmonic second sound, and the changes in the cardiac silhouette to be described, suggests that the acute phase of bagassosis is associated with the development of a transient pulmonary hypertension. Intradermal tests for tuberculosis, histoplasmosis and coccidioidomycosis are usually negative. Examinations of the sputum are negative for tubercle bacilli, pathogenic fungi and harmful bacteria.

Roentgenograms of the chest characteristically disclose the presence of miliary shadows symmetrically distributed throughout both lungs, which do not differ in any way from the appearance of typical miliary tuberculosis. Other roentgenographic patterns are observed less frequently and may include large patchy areas of bronchopneumonic infiltration, linear streaks radiating outward from the hilar zones, and the presence of a diffuse "ground glass" haze overlying the lung fields. Lesions are usually more prominent in the hilar areas and at the lung bases. The apices are often spared. Enlargement of the cardiac shadow may be noted, with particular prominence of the pulmonary artery segment.

The vast majority of patients tend to improve spontaneously when they are removed from contact with the offending agent. Symptoms gradually abate in a few weeks and complete recovery usually takes place in one to six months, although in some cases the patient may not feel entirely well for a year or more. The abnormal x-ray findings gradually resolve and as a rule no trace of the disease remains after two to six months, but some impairment of pulmonary function may be detected for longer periods.

Four of the fifty-three patients reported in the literature have died of bagassosis, representing a mortality rate of about 7.5 per cent. However, this figure is probably not a true one and should be much lower since many milder cases of the disease have undoubtedly escaped medical attention.

The diagnosis of bagassosis is based on the occupational history, the characteristic clinical and roentgenographic picture, the usual benign

course and the exclusion of other disorders. Miliary tuberculosis offers the chief problem in differential diagnosis. However, any of the vast group of diseases which may be associated with miliary lesions in the lung must be considered and excluded [*29*].

PULMONARY FUNCTION

The clinical features of bagassosis clearly indicate that this condition produces a marked derangement of the respiratory mechanism. Dyspnea is the most characteristic symptom and may be alarming in its severity, even when radiographic findings are not pronounced. Cyanosis occurs and is sometimes unrelieved by the administration of oxygen. In addition, shortness of breath may persist for months or even years after all other signs of the illness have disappeared.

Like its etiology, however, the nature of the functional disturbance has remained obscure. The possibility of an alveolar capillary block appears to deserve some consideration because of the clinical similarity of bagassosis to other conditions, such as the Hamman-Rich syndrome and berylliosis, in which this mechanism is known to be involved. Although pathological information is scanty, the available description of a "fibroblastic reaction of the interstitial tissue" [*8*] is also compatible with disturbances of gas exchange at the alveolar-capillary level. Sodeman and Pullen [*8*] concluded that "the clinical picture, from the striking dyspnea to the later polycythemia may be explained as due to the effects of this reaction and the anoxia resultant therefrom." On the other hand, the clinical and pathological evidence [*20,21,26*] pointing to the presence of bronchiolar obstruction secondary to bronchiolitis suggests that alveolar hypoventilation might ensue and, indeed, the finding of respiratory acidosis in this disease tends to support this possibility.

Most of the cases of bagassosis which have appeared in the literature were reported prior to the present era of rather intense interest in pulmonary physiology. As a result, no significant attempts have ever been made to measure the impairment of ventilatory or respiratory function produced by the disease. Two authors [*8,11*] have carried out determinations of the vital capacity in a few patients. In all cases the vital capacity was abnormally low and the reduction persisted in some degree for long periods, even after considerable clinical improvement had occurred and marked roentgenographic resolution had taken place.

Two patients in the present series had pulmonary function studies performed during the acute phase of their illness, during the convalescent period, and at intervals of eleven and twenty months after recovery. The results of these studies are summarized in Tables I and II.

In W. R. (Case II), who suffered from relatively mild disease and whose symptoms were already subsiding at the time of admission, pulmonary function studies were carried out approximately one month after the onset of his illness. The vital capacity was reduced by one-half of the predicted normal and the maximum breathing capacity was decreased to 68 per cent. Nearly two months later the arterial oxygen saturation was still significantly lowered (91 per cent) while breathing room air, but rose to 100 per cent on pure oxygen.

R. F. (Case III) appeared to have a mild form of bagassosis insofar as roentgenographic changes were concerned, but he complained of extreme dyspnea. Pulmonary function studies were performed at the height of his illness. The vital capacity and timed vital capacity were only slightly lowered, but the maximum breathing capacity was reduced to 51 per cent of the predicted normal. As in Case II there was marked lowering of the arterial O_2 saturation (90.8 per cent).

Both patients exhibited gradual improvement in pulmonary function as clinical recovery took place, and all determinations were completely within normal limits eleven and twenty months later in the respective cases.

We are well aware that these studies in no way provide a complete evaluation of the abnormal pulmonary physiology produced by bagassosis, but at least they represent one further step in the understanding of this disease. A disturbance of ventilatory function is indicated by the lowered vital capacity and maximum breathing capacity and is compatible with the presence of airway obstruction such as might be produced by bronchiolitis. Unfortunately, physiological data pertaining to diffusing capacity, residual volume and measurements of intrapulmonary mixing of inspired gas cannot be offered at this time. In the absence of these determinations, no further conclusions seem justified and it cannot be definitely stated whether or not some degree of alveolar-capillary block may occur, but the present evidence, how-

ever meager, does not tend to support such a mechanism. It must remain for future and more complete studies to elucidate further the physiological defect in bagassosis.

THERAPY

Treatment of the recorded cases of bagassosis has usually included hospitalization, which effectively removes the patient from occupational exposure and allows spontaneous recovery to take place. Nothing more is necessary in most instances. In fact, merely changing the patient's place of work to another part of the factory where exposure to bagasse dust is obviated has been successful in controlling symptoms in many cases. Prophylactic measures directed at dust control, such as improving ventilation, wetting the bagasse, and the utilization of masks, have apparently accounted for a reduction in the incidence of the disease. The use of "dehydrated" bagasse which has most of the fine particles of dirt removed, leaving chiefly the larger fragments of cane, is also said to be less hazardous [*11*]. Nonetheless, as we previously pointed out, sporadic cases continue to occur.

Since the fundamental cause of bagassosis has not yet been pinpointed there is no specific treatment for the disease. Although Singh [*15*] reports "very quick" and "marked" improvement following the administration of penicillin and "anti-allergic drugs" he does not further characterize the latter agents. Ganguly and Pal [*14*] have also indicated a response to penicillin, but others [*11,12*] have not confirmed these results. In addition, some of Singh's patients may have suffered from conditions other than bagassosis. Our own experience and other reports from the literature have indicated that the various antibiotics and the sulfonamides have no significant beneficial effect. Several of Sodeman's and Pullen's [*8*] patients improved after receiving potassium iodide, but it is doubtful that this therapy had a specific effect and it seems more likely that spontaneous recovery took place.

When the illness is pronounced, symptomatic therapy is very beneficial. Codeine is effective in the suppression of annoying cough and oxygen usually relieves cyanosis and dyspnea. However, in some cases, when symptoms are particularly severe and progressive, even oxygen and intermittent positive pressure breathing will not completely relieve the air hunger. It is in situations of this kind that the adrenal steroids appear to be indicated. Cases I and III of this report are the only ones in which the use of steroid therapy has been recorded. In Case I, cortisone and ACTH were employed for only a brief period; however, these agents were given at the height of the disease when the patient's condition appeared critical and the dramatic clinical improvement which followed can hardly be attributed to any other cause. There is no doubt in our own minds that this therapy preserved the patient's life. R. F. (Case III) received prednisone for nearly two months as his sole medication. He exhibited prompt and significant clinical improvement but we have no way of knowing whether this was an effect of steroid therapy or the result of spontaneous improvement. Nonetheless, we feel that our experiences certainly justify further trial of adrenal cortical therapy in the future, especially in the severer forms of bagassosis.

SUMMARY

1. The historical features of bagassosis are reviewed and supplemented by previously unreported data. A case report is presented which is believed to represent the first recognized instance of the disease.

2. Current etiological, pathological and therapeutic concepts, and the clinical characteristics of bagassosis are discussed in the light of a review of approximately fifty-three cases reported in the world literature, the four patients presented in this paper, and some twenty other cases observed by one of the authors.

3. Three new cases, which have been collected since 1954, are described in detail. Two of these patients were the first to undergo pulmonary function studies. While certain findings appear to be compatible with the presence of alveolar hypoventilation secondary to bronchiolitis, more complete studies are necessary to elucidate further the physiological defect in this disease.

4. Two of the patients herein discussed were the first to be treated with adrenal steroids. The striking beneficial effect of this therapy in one instance suggests that these agents may be life-saving in the severer forms of bagassosis. The apparent clinical response of the second patient, with a milder form of the disease, is more difficult to evaluate but certainly seems to justify further trials of steroid therapy in the future.

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Sociologic, Psychologic and Metabolic Observations on Patients in the Community of a Metabolic Ward*

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THERE is abundant experimental evidence that life experiences as interpreted by the highest centers of the brain are capable of affecting a large number of bodily mechanisms. Thereby stimuli which owe their force to their significance to the individual are capable of producing many symptoms and manifestations of disease. Among such manifestations are changes in the urinary excretion of certain metabolites in man, as reported by Schottstaedt and associates [*1*]. They found that persons who responded to situations by preparation for short violent action, such as for fight or flight, or by tempestuous or aggressive behavior with feelings of excitement, intense anger or apprehension, demonstrated a diuresis of sodium and water. Situations which evoked listless behavior, reduced activity, slowed and decreased speech with attitudes and feelings of despair, hopelessness or depression were associated with retention of sodium and water. On the other hand when threatening situations elicited restless behavior, increased alertness and readiness for action with mixed feelings of confidence and tension a biphasic reaction occurred. Initially renal excretion of water and sodium was decreased but diuresis of water occurred as the tense situation subsided.

The present report concerns a pilot study designed to extend as well as to strengthen earlier data. The opportunity to carry out intensive studies of patients on "balance" regimens in the community of a research hospital ward permitted not only detailed metabolic and psychologic evaluation but also made it possible to include data on the social dimension.

METHOD

The study was carried out on a metabolic ward in a research hospital, an environment usually considered "neutral." Observers included five doctors, two of whom were psychiatrically trained, a medical student and a sociologist. The latter lived in the hospital for eleven weeks as a patient without the other patients being told of her role as an investigator.

The whole population of a metabolic unit of twelve beds was studied in the manner of an anthropological investigation of a community. The values, behavior patterns, social hierarchy and vulnerabilities were investigated in terms of the patient group, the nurse group and the physician group as well as of the ward community as a whole. In addition, individual psychological studies of the patients were carried out with emphasis on life experience, past attitudes and behavior patterns and the individual's behavior in relation to his illness and to other members of the ward community.

The chemical data were gathered from analyses of complete urine and stool collections from patients on "balance regimens," who received precisely the same food and water every day weighed to the fraction of a gram. The chemical constituents of the food were periodically analyzed. Although the precision of the chemical measurements could not be matched, a careful attempt was made to pinpoint sociologic stresses and psychologic conflicts and to define the adaptations of the individuals to one another and to the community of the ward.

Data on potentially stressful situations were gathered and classified roughly in three categories:

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(1) Situations arising from interactions within the community. (2) Situations originating from without but affecting relationships in the community. (3) Personal situations in the lives of each of the patients related to their outside life and not directly affecting the ward community. The sociologist residing on the ward kept a diary containing a description of each patient's behavior from day to day with direct quotations from conversations and accounts of interviews with the various patients. Only at the end of the study, after the social and psychological data had been integrated and the evaluation recorded, were the presumed stressful events correlated with the chemical data.

The metabolic ward is in a separate building on the campus of the Medical Center at Oklahoma City. It is attractively appointed and would be considered luxurious by most of the patients. The potentially stressful significance of events to these patients was evaluated on the basis of a careful personality appraisal of each of them from interviews, discussions of dreams and observations of behavior by the various observers. It is emphasized that these judgments were made separately and the data kept separate from the metabolic measurements. The chief deviations in the latter included retention of or diuresis of sodium, potassium, chloride, nitrogen, creatinine and water. Metabolic data are expressed in terms of standard deviations from a control level. This avoids the introduction of multiple units of measure and permits the significance of any deviation to be determined at a glance. A positive balance indicates retention or reduced excretion of the substance studied. Days on which the subjects were not under the influence of changes in pharmacodynamic agents and which were judged to be relatively free of stress were designated as control days. Averages and standard deviations were calculated from control days during which intake and activity were the same as occurred on the day of the stress under consideration.

RESULTS

Ward Atmosphere. The atmosphere of the ward was usually a relaxed and pleasant one. The ambulatory patients were encouraged to wear street clothes, to eat their meals together in a dining room, and to visit in one another's rooms. They were allowed to leave the hospital if the protocol of their studies permitted. There was a strong group feeling which seemed to be based on the sharing of common experiences in the same milieu. New patients who entered the hospital feeling a little frightened and insecure, knowing that they had serious illnesses and that relatively new medications would be given to them, were usually reassured by the older patients. Evidence of improvement in any patient was welcomed by the group who seemed to have considerable sympathy for one another. Many regarded the ward as "home." One said, "It's peaceful here; like a retreat"; several commented on the intense interest of the doctors in the personal needs and feelings of the patients. The nurses and dietitians radiated an attitude of warmth and acceptance. One said that she prayed every night for the wonderful people who were patients on the ward.

When a new patient appeared on the ward the older patients usually did not ask questions about background, either social or economic. Discussion centered about symptoms. If the new patient was reticent, few direct questions were asked. If he wanted to talk, however, there usually ensued a detailed discussion of diagnoses, plans of study, length of stay and similarities of illness to those of other patients on the ward. Unusual signs and symptoms or unusual laboratory procedures aroused considerable interest. There was much discussion among the patients of the rigid routine involved in a balance study. New patients were very thoroughly indoctrinated by their fellows into the rigid rules of the metabolic regimen. In this way the new patient learned to de-emphasize previous experience, being simultaneously introduced to a value system which placed great emphasis upon illness and precision in the collection of excreta.

The atmosphere on the ward was not accidental. It was carefully promoted by the head nurse who worked actively to maintain it. Having previously been in charge of a similar metabolic ward, she came to the Foundation before the building was completed and helped with all aspects of establishing the ward. With deep personal interest in the institution she handled matters with restraint and sympathy but always firmness. Although the patient found himself in an environment governed by rules and by the clock, tension and pressure were usually at a minimum.

Interpersonal Attitudes Among the Patients. Despite the friendly and accepting atmosphere of the ward, new patients soon learned that certain things were disapproved of by the community of patients, nurses, dietitians and ward attendants. These included unneccessary noises or disturbances, any criticism of the ward or staff, or any rebellion against the routine. The personal traits which appeared to favor a good adjustment on the ward included a certain amount of passivity and ability to conform to the rigid routines easily and without undue complaint. Reluctance on the part of ambulatory patients to mingle with others was a cause for mild disapproval. When patients complained or expressed more concern about themselves than the group thought justified, they were criticized by the others and often teased. If a new patient tried to dominate the situation before he had been accepted by patients already on the ward, he was effectively ignored by them.

It was striking that prestige among the group was not conferred according to the usual criteria which obtained just outside the door of the hospital but according to special circumstances peculiar to that community. At various times a banker, a college president and a millionaire industrialist were hospital-

ized and found to have less status in the group than those who were much lower in the social scale outside the hospital. The factors which seemed important in determining the prestige of an individual on the ward were:

(1) Length of hospitalization: With increasing length of stay, the length of time spent on a balance regimen became a prestige point, as well as the number of transfusions, the length of time a gastric tube had been in place, or even the size of a spleen. These items continued to be a matter of pride on follow-up visits after discharge.

(2) Type and severity of illness: As already implied, having a rare disease or unusual physical finding was a major prestige item but even more important was the severity of the illness. There appeared to be some feeling that those who did not have fatal diseases were making a lesser contribution to science.

(3) Conformity to routines: As pointed out earlier, adherence to the rigid balance regimen was highly valued by the patients. Those who had considerable difficulty in conforming initially were able to acquire prestige if they mastered the routine within a reasonable time. The prestige of those who became lax declined correspondingly.

(4) Responses to therapy: Dramatic response to therapeutic maneuvers was looked upon as a sign of success for the ward and thereby increased the patient's status.

(5) Personality: Congeniality and forcefulness of personality without obvious aggressiveness were highly regarded among the patients. Those who participated most in group activities were correspondingly esteemed by the group.

(6) Talents: In addition to the factors listed, personal talents seemed to be of some importance with respect to group standing. One of the patients seemed to gain prestige by her ability to sew and by having won a trophy for a bedspread she had made. Another gained prestige by his oil paintings which attracted the attention of the newspapers. A third patient was admired for his excellence at dominoes.

Most of the patients adjusted to the ward quite easily and were accepted by the other patients and ward personnel. The few deviants who did not adjust easily pointed up the important elements of acceptance on the ward. One example was provided by a Mrs. K., a patient with leukemia, who spoke constantly of how lonesome she was and how she longed to see her grandchildren. After the first polite acknowledgement of her loneliness, the patients ignored her. One of them said, "What does she think they will do when she dies?". Another said, "I have children at home and I don't talk about them all the time." Unable to take part in ward activities, Mrs. K. soon found herself isolated from the other patients. Within two weeks she left saying she could not conform to the ward routines; but her rejection by the other patients appeared to be a major factor in her decision.

Metabolic Studies. The importance of the atmosphere of the ward is indicated by the correlation of metabolic data with the events which occurred in the course of this study. Following a brief period of minor confusion in getting the study underway, there was a period of three weeks when days went by quietly and smoothly. Following this, there was a week in which several disrupting events occurred. It was at the time of the Thanksgiving holidays. Several patients left to be with friends and family for part of the day. Those remaining felt somewhat lonely and depressed. During this same week three patients were discharged and a fourth was making preparations to leave. Two of the remaining patients seemed to be terminal cases. One of them did die within a week and the other was so ill that he asked that none of the other patients visit him. The discharges enabled two of the patients who had been sharing a room to separate. This seemingly unimpressive event aroused strong feelings in one of them and occasioned an incident referred to below as episode 3. This period was one of considerable turmoil on the ward. The smooth structure which had been in evidence previously seemed to disintegrate.

A week later, however, tensions decreased and the ward seemed to be running smoothly again. The comparatively stable atmosphere continued for the next ten days. On December 13 the atmosphere again became troubled when one of the nurses reprimanded two patients for leaving the ward and going to a candy vending machine. This incident is described as episode 4. A sensitive issue had been introduced, that of adhering to dietary proscriptions. This event served to initiate a period of emotional turmoil which continued until Christmas. Difficulties were aggravated by the admission of three new patients who did not fit well into the social pattern of the ward. One of them, a man with an anxiety state, frightened one of the old patients, who feared he might go crazy, to such a degree that he kept his light on at night. Another new patient was unduly garrulous and non-conforming and the third was dull and circumstantial.

The number of days that were judged stressful for the individual patients was, of course, greater during the two periods of turmoil than during the periods of comparable length when the atmosphere of the ward was relatively stable and serene. It was striking, however, that a greater percentage of individual stressful experiences were associated with significant metabolic deviations during the periods of turmoil on the ward than during the calm periods. There were 213 patient days of suitable balance data during the whole period of study. On 103 of these days the ward was judged to be quiet and on 110 it was considered disturbed. Twenty-five of the presumed individually stressful experiences occurred when the ward was quiet and forty-two when it was disturbed. Only twelve (48 per cent) of the stressful events occurring during the quiet period were found to have been ac-

companied by significant metabolic alterations; however thirty-six (86 per cent) of the stressful events occurring during the disturbed period were accompanied by metabolic alterations of significant degree. (Table I.)

In the course of this study there were metabolic data for 146 patient-days which were not considered to be stressful. Significant metabolic deviations occurred on twelve of these days. (Table I.) Four of them involved the metabolic data of Mrs. P. on the four days subsequent to episode 1, to be described. Although in the record we had not designated those days as stressful they probably should have been because Mrs. P. was relatively taciturn and complained of a continuous headache. Three of the remaining significant deviations on non-stressful days occurred during periods of relative calm on the ward and five when the general ward atmosphere was disturbed.

TABLE I
STRESSES OCCURRING ON A METABOLIC WARD

	Ward Atmosphere		
	Quiet	Disturbed	Total
Stressful days on which metabolic data were available	25	42	67
Non-stressful days on which metabolic data were available	78	68	146
Total patient-days on which metabolic data were available	103	110	213
Stressful days with significant metabolic deviations	12	36	48
Non-stressful days with significant metabolic deviations	7	5	12
% of stressful days with significant metabolic deviations	48	86	72
% of non-stressful days with significant metabolic deviations	9	7	8

Balance data on non-stressful days selected as "controls" were relatively stable. Table II is illustrative of such a steady state, showing only minor fluctuations in either direction.

Examples of deviations observed on stressful days are presented herein:

Episode 1: Mrs. P., who had been on the ward for two years, had xanthomatous biliary cirrhosis. She enjoyed great prestige which derived not only from her length of stay but from her unusual ailment. When, after two years, another patient, Mrs. D., was admitted to the ward with the same disease, Mrs. P. felt somewhat threatened, especially since Mrs. D. had a commanding personality and seemed to be competing with her. Both Mrs. D. and Mrs. P. were scheduled to receive ACTH on November 9. Mrs. P.'s therapy was delayed, however, and Mrs. D. was treated first. The following morning Mrs. D. came to breakfast wearing earrings and a choker. She seemed in better spirits than usual and commented that she had not worn jewelry since she first noticed lumps appearing on her face. She made frequent comments during the day about "poor" Mrs. P. who for her part was angry and depressed, complaining bitterly of feeling ill. On November 14, Mrs. P. admitted, in a sudden outburst, "I see Mrs. D. and she's so much better it almost kills me." Metabolic balance studies showed marked fluctuations for both patients. (Table III.) The balance data for November 10 show deviations which are similar for the two patients despite the fact that Mrs. D. had begun her ACTH the preceding day and Mrs. P. had not. The similarity in sodium excretion for the two patients is most striking, and consistent with the fact that both were reacting in a highly aggressive fashion, although one was exultant and the other angry.

TABLE II
METABOLIC DATA ON A NON-STRESSFUL DAY*

Date	Patient	Balance Data (S.D.)						Excretion	
		Na	K	Cl	N	Ca	P	Creatinine	Volume
12/4	Mrs. P.	+1.1	−0.9	+0.6	+0.2	+0.5	+0.2	+0.1	−0.8
	Mr. H.	−0.6	+1.5	−0.3	−0.5	−0.4	0	−0.4	+1.1
	Mrs. D.	+1.6	+0.6	+0.6	−1.7	−0.4	+0.7	−0.7	+0.9
	Mr. T.	+0.8	+0.9	+0.6	−1.0	+0.7	+1.5	+1.7	−0.5

* Units expressed in terms of standard deviation from means of controls.

TABLE III
METABOLIC FLUCTUATIONS (S.D.) ASSOCIATED WITH PATIENT COMPETITION (EPISODE 1)

Date	Patient	Balance Data (S.D.)						Excretion	
		Na	K	Cl	N	Ca	P	Creatinine	Volume
11/9	Mrs. P.	−2.3	+1.6	−4.3	+2.8	−1.2	+2.2	+1.0	−0.1
	Mrs. D.	−1.7	−1.5	+0.8	0	+1.5	−1.1	−0.6	+0.9
11/10	Mrs. P.	−5.0	+0.4	−6.8	+1.0	−1.8	−1.3	+2.4	−0.9
	Mrs. D.	−4.1	−1.5	−1.3	+4.9	+1.2	+0.7	+1.6	+0.6

Episode 2: Mr. H. was a thirty-five year old patient who had had rheumatoid arthritis for eighteen years. His joints were rigidly fixed so that he could neither sit nor turn his head. He could move some of the

TABLE IV

METABOLIC FLUCTUATIONS NOTED IN MR. H. (EPISODE 2)

Date	Balance Data (S.D.)						Excretion		Remarks
	Na	K	Cl	N	Ca	P	Creatinine	Volume	
11/6	+0.9	+2.0	+0.3	+4.4	+0.7	+2.3	+8.0	+0.3	Given postcard
11/18	+1.9	+0.7	+1.8	+0.4	−2.0	+0.1	+1.3	+0.3	Joking with Miss R.
11/24	+3.0	+2.2	+3.3	+7.1	+4.5	+2.5	+2.7	+3.5	Rebuked by Miss R.
12/21	−8.4	−5.4	−3.1	−4.1	−0.6	−10.9	−1.3	−2.4	Rebuked by Miss R.
12/22	+2.6	+0.2	+2.4	−2.0	−0.2	−1.1	−1.0	+0.9	Brooding
12/23	+9.2	+3.8	+4.2	−2.0	−0.6	−4.2	+0.7	+3.2	Remorseful
12/27	+8.6	+0.2	−4.1	−0.6	−0.8	−2.2	−0.5	−2.9	Trying to please Miss R.

fingers of his right hand but otherwise his joints were not capable of independent motion. Despite this, and after seven years of immobility, he had forced himself out of bed, had taken correspondence courses in radio and television, and had taught himself oil painting. He was proud of his accomplishments and had little sympathy for those who did not share his high standards. Independence was a matter of considerable concern to him. When Miss R., who had arrived on the ward a few days before, gave him a penny post card, he was quite incensed and told the nurses bitterly that he did not need anyone's charity. Soon, however, he and Miss R. were on friendly terms, which included a great deal of joking and teasing, but in which he also confided to her his hopes for the future and his feelings about other patients on the ward. He evidently prized Miss R.'s approval and treated her with gallantry and affection. During the course of the study Mr. H. showed a number of fluctuations in balance which seemed to be related to situations involving himself and Miss R. On November 18, when there was more than the usual amount of joking between the two, the balance data showed a retention of sodium, chloride and calcium. On November 24 Miss R. felt that Mr. H. was becoming "too fresh" in his comments and a little too friendly. In trying to stop this without hurting his feelings, she said she would not talk to him for the rest of the evening. He seemed dejected by this rebuke. About the middle of December a new patient was admitted, an aggressive woman who used more makeup than the other women patients on the ward and had difficulty in adjusting to the ward atmosphere. She constantly worried about her husband and whether he was being faithful to her. Mr. H. teased her considerably about this and on occasion made rather vulgar comments to her. During this period the relationship between Mr. H. and Miss R. became strained. On December 21 Miss R. rebuked Mr. H. for the way he was talking to the new patient. He admitted that his comments had been in poor taste but defended himself by saying that she had "egged him on to it." The following day he seemed to be brooding over the rebuke and it was thought that he was angry at Miss R. On December 23, however, he expressed guilt and remorse at what he had said and the way he had acted. On all three of these days his balance data showed striking fluctuations. There was a marked diuresis for most of the substances studied on December 21, the day of the initial rebuke, and this was followed on the two subsequent days by marked retention of sodium, potassium, chloride and water. On the first of these days marked feelings of guilt had been aroused and on the two subsequent days there was considerable brooding. By December 27 he was asking Miss R. if they could not be friends again but specifically requested that they no longer tease or joke with each other. In examining the fluctuations recorded in Table IV it should be noted that the general atmosphere of the ward was comparatively calm on November 6 and 18, was somewhat disturbed on November 24, and was markedly disturbed on the dates noted in December. It is interesting that the more striking deviations from a true balance occurred at times when the ward was in a disturbed state. The stresses which occurred while the ward atmosphere was quiet did not show deviations of such a marked degree. Whether this was related to the ward atmosphere in which the stresses occurred or to the intensity of the stresses is not certain.

Episode 3: Another interesting relationship which existed on the ward was between Mr. H. and Mr. T. Mr. T. was a patient with hypopituitarism resulting from a chromophobe adenoma which had been surgically removed two months before the present studies. His deficiency was manifested chiefly by myxedema. He was somewhat overweight, flabby, walked with a lumbering gait, and talked in a slow, deliberate drawl. He had very few friends outside the hospital, although he was very well liked within the hospital. He enjoyed Mr. H.'s companionship particularly. During

the first month of the study these two patients shared a room. Mr. H. felt handicapped in his painting, however, because of the close quarters and the fact that Mr. T. frequently touched his painting and smeared it. Other irritations arose because Mr. H. prized his privacy and independence. Toward the end of the first month when vacancies developed among the rooms on the ward, Mr. H. asked that he be given a separate room. He felt some apprehension about making this request lest it be refused. However, on the first day of December he was moved to a separate room where he was once again able to paint in the privacy he wanted. Mr. T. was depressed and lonely. He had spoken repeatedly of how much Mr. H. needed him and therefore felt keenly this loss of status. During the next few days he frequently remarked at how he missed his "old buddy" and hoped they would be put in a room together sometime in the future. Both of these patients showed deviations in balance data during these two days as shown in Table v. It was particularly striking to observe that alterations appeared to occur so readily in response to stress in a man with grossly impaired pituitary function who had undergone surgical ablation of the gland.

TABLE V
METABOLIC FLUCTUATIONS ASSOCIATED WITH A CHANGE OF ROOMS (EPISODE 3)

Date	Patient	Balance Data (S.D.)						Excretion	
		Na	K	Cl	N	Ca	P	Creatinine	Volume
12/1	Mr. H.	+0.2	−0.8	−1.5	+0.3	+0.7	+0.8	+0.2	+0.8
	Mr. T.	+1.0	+2.2	+1.5	−0.3	−0.1	−0 1	+4.7	*+2.6*
12/2	Mr. H.	+0.6	+1.3	+0.7	+2.2	+1.3	+0.3	+1.4	+1.9
	Mr. T.	+1.0	+2.2	+1.5	+2.6	+0.1	+1.7	+3.0	+0.3

Episode 4: On December 13, an interchange occurred between these same two patients and one of the nurses which brought ward frictions into the open and precipitated the second period of unrest on the ward. Mr. H. and Mr. T. were discovered at a candy vending machine by a nurse. She told them they were no more reliable than children and sent them back to their rooms. It was established that neither of the men had actually eaten any candy although they did get chewing gum. Mr. T was openly resentful of the nurse's manner and repeatedly complained about the episode that afternoon and the following day. Mr. H. seemed to feel guilty and resentful and withdrew from participation on the ward. Data obtained on December 13 and 14 for these two patients are given in Table vi. Interpretation of metabolic data obtained on Mr. H. December 14 is complicated by the fact that he was seen by the orthopedic resident on this date for evaluation for surgery. He was disappointed that the senior surgeon had not visited him and he was greatly concerned about the possibility of surgery. These feelings were added to those already aroused by the nurse's reprimand.

TABLE VI
METABOLIC FLUCTUATIONS ASSOCIATED WITH REPRIMAND BY NURSE (EPISODE 4)

Date	Patient	Balance Data (S.D.)						Excretion	
		Na	K	Cl	N	Ca	P	Creatinine	Volume
12/13	Mr. H.	−2.0	−3.8	−2.8	−2.3	+0.8	−1.3	−0.6	−0.6
	Mr. T.	+1.8	+1.6	+1.7	0	−1.5	+0.4	+1.0	+0.6
12/14	Mr. H.	−1.0	+1.0	−1.1	+2.0	+1.1	+1.9	+2.4	−0.5
	Mr. T.	+1.8	+1.6	+1.6	+1.9	−1.5	−1.2	+3.7	+2.2

Episode 5: It was of interest that ward routines usually taken as a matter of course by the staff occasionally had a disturbing effect on patients. Thus, ward rounds were ordinarily a matter of little concern. Mrs. P. who usually accepted them easily seemed restless and more irritable than usual on December 17, when the ward was generally disturbed, and complained at this time of the long wait before her turn. Data for this episode are given in Table vii. No specific personal conflict was elicited for that day and it may be that her disturbed state was related to the generally disturbed condition of the ward. In any case there were significant alterations in the metabolic data, as shown in Table vii.

Episode 6: At Christmas time, a volunteer spent part of each day with the patients helping them make Christmas decorations and simple gifts. The volunteer first appeared on December 1, one of the days when the ward was disrupted by discharges and illnesses. Mrs. P., who joined in the Christmas preparations, was extremely critical of the volunteer and implied that she had handled the day's activities very poorly. During this day when she was angry and irritable Mrs. P. showed significant metabolic deviations which are recorded in Table vii.

Episode 7: Mr. H. had been on preliminary balance studies for several weeks prior to a trial of several pharmacodynamic agents. Although specifically told that the agents were not being given primarily for their therapeutic efficacy but for study of their metabolic effects, he yet was anticipating beneficial results from their use. The first tablets given him were placebos. When, after what he thought a reasonable length of time, he had still noted no effect from them, he became discouraged and depressed. He spoke of leaving at once if the agents to be used had no more effect than this one. The metabolic deviations observed under these circumstances are shown in Table vii.

TABLE VII
METABOLIC FLUCTUATIONS ASSOCIATED WITH WARD ROUTINES (EPISODES 5, 6, 7, 8)

Date	Patient	Balance Data (S.D.)						Excretion		Remarks
		Na	K	Cl	N	Ca	P	Creatinine	Volume	
12/17	Mrs. P.	+2.0	+0.1	+2.1	−2.3	+0.9	−2.2	+1.0	+1.9	Rounds
12/1	Mrs. P.	+0.5	−0.2	+0.8	−2.6	+8.0	−0.3	−1.0	−1.3	Christmas preparations
11/2	Mr. H.	+2.4	+1.0	+2.4	−1.6	−1.3	−1.3	+2.0	+2.3	Medication "unsuccessful"
1/1	Mr. B.	−0.5	+2.8	−0.3	−5.0	+0.1	−0.4	−0.7	−1.8	Lack of privacy

Episode 8: Another type of reaction to ward routines was demonstrated by Mr. B. who became exasperated because the ward routines requiring the nurses to come in and out of his room deprived him of privacy. His irritation became evident on a day when he had no one to complain to because both his physicians were out of town. He felt deserted and exploited and was querulous and resentful most of the day. The deviations in his balance data are shown in Table VII.

TABLE VIII
METABOLIC DEVIATIONS ASSOCIATED WITH ANXIETY AMONG THE NURSING STAFF (EPISODE 9)

Date	Patient	Balance Data (S.D.)						Excretion	
		Na	K	Cl	N	Ca	P	Creatinine	Volume
1/7-8	Mr. B.	−8.4	+2.1	−1.0	+0.8	−3.5	−6.1	+2.6	−2.9
	Mrs. D.	−8.1	−0.2	−6.0	0	−1.6	−0.5	+0.6	−0.6
	Mr. H.	−1.5	−1.7	+0.4	−1.0	+0.1	.....	−1.0	+0.3
	Mr. T.	−4.0	+1.3	−6.9	−3.2	+0.1	−4.3	+1.7	−2.9

Episode 9: The effect of ward atmosphere and the potency of non-verbal communication between staff and patients was vividly demonstrated by a situation which developed toward the end of the study. Prominent in the value system of the nurses was an emphasis on impartiality in considering and dealing with patients, physicians or other nurses. On one occasion the nurses were given a questionnaire in which they were asked to state confidentially their preferences among patients and staff. This information was to be used in evaluating prestige and interpreting individual interpersonal reactions which had been noted. Tensions mounted among the nurses as they discussed with each other this new turn of events. Should they answer the questions? Could they honestly express preferences without opening themselves to censure? What would really be done with their answers? Finally, on January 7, one of the nurses went to the chief nurse to resign, and another asked if she might be permitted to take her vacation early, since she was "nervous and distraught." The nursing staff continued to be disturbed until the questionnaire was withdrawn the following day. The anxiety felt by the nurses seemed to be transmitted to the patients although they knew nothing of the questionnaire. The co-author who was living on the ward knew nothing of this part of the study. She noted the tension of the nurses, however, and felt an apparent covert hostility towards her. It was striking that all patients who were on metabolic study at the time showed a consistently negative sodium balance during this two day period. Other balances were predominantly negative as shown in Table VIII. Mr. H. reacted outwardly by being much quieter than usual. Mr. T., on the contrary, spent two days making unkind comments to and about others, which was quite unlike his usual careful manner. He stated frankly, "I feel mean." Mr. B. was particularly resentful and commented that the nurses were much more brusque in talking to him and their admonitions to relax seemed to him to evidence a lack of interest in him personally. Despite individual differences in reaction, the general upheaval of the ward was evident in everyone's behavior. The night nurse complained that she had never had so much trouble getting the ward quiet for the night. Everyone seemed more ill and more demanding than usual.

Influences Outside Ward. Visits by family members or brooding over family troubles accounted for the majority of metabolic fluctuations associated with influences off the ward. Early in the study Mrs. P. was visited by her mother and daughter. Her mother told her they might be forced to leave their home and she did not know where they would go. This was very disturbing to her and was reflected in marked deviations in balance. (Table IX.) Mr. B. showed deviations in balance data quite regularly when visited by his wife. On one visit she infuriated him by telling him that her father, on hearing he was in a hospital, assumed it was a mental hospital and asked if he were "locked up." On Thanksgiving, with several of the

TABLE IX

METABOLIC FLUCTUATIONS ASSOCIATED WITH INFLUENCES FROM OUTSIDE THE WARD

Date	Patient	Balance Data (S.D.)						Excretions		Remarks
		Na	K	Cl	N	Ca	P	Creatinine	Volume	
11/7	Mrs. P.	−14.0	+0.5	−5.3	+1.6	+0.6	−2.0	+1.1	+0.7	Visited by mother
12/7	Mrs. P.	−2.4	−1.7	−2.1	−0.3	+1.4	+0.1	0	−2.0	Brooding over family troubles
12/18	Mr. B.	+3.4	+0.7	+2.7	0	−0.3	−0.6	+0.7	+2.8	Visited by wife
12/23	Mr. B.	−1.8	−0.4	0	−2.9	−0.5	−1.0	+0.2	−1.1	Visited by wife
12/30	Mr. B.	−0.5	+2.8	−0.3	−5.0	+0.1	−0.4	−0.7	−1.8	Visited by wife
11/25	Mr. H.	−1.4	−2.8	−2.1	−3.6	−1.0	−0.8	−6.5	−2.2	Talking about home

patients out for the day, Mr. H. became rather nostalgic and talked about going home. On all these occasions, deviations in metabolic balance were noted. (Table IX.)

Stressful Events not Associated with Metabolic Deviations. Three deaths occurred during the course of these studies; only one was associated with metabolic deviations among the remaining patients. None of the three who died had played a prominent role on the ward and none had formed close ties with the others. Two of the deaths occurred during periods in which the ward was functioning smoothly.

A day was designated as stressful for Mrs. P., when she could not find money she had collected from selling Christmas cards. She became intensely agitated and insisted that someone had stolen the money until she found it later that day where she had hidden it. No significant metabolic deviations were noted for this day.

TABLE X

SUMMARY OF STRESSFUL EVENTS ASSOCIATED WITH SIGNIFICANT METABOLIC FLUCTUATIONS (>2.0 S.D)

Patient	Patient-days Included	Situations Arising		Total
		On Ward	Off Ward	
Mr. H.	59	15	1	16
Mrs. P.	54	6	3	9
Mrs. D.	58	8	2	10
Mr. T.	16	4	0	4
Mr. B.	26	5	4	9
Total	213	38	10	48

On December 1, when Christmas preparations were begun, Mrs. D. refused to participate because of her religious beliefs. There was considerable consternation over this and many deprecatory remarks were made, some to her and others about her. This was recorded as a stressful occasion for her but no significant metabolic fluctuations were noted.

TABLE XI

SUMMARY OF STRESSFUL EVENTS ASSOCIATED WITH SIGNIFICANT METABOLIC FLUCTUATIONS

	On Ward		Off Ward
Interpersonal reactions	20	Family	8
Treatment and routines	14	Business	1
Other	4	Other	1

On December 9 Mr. T. expressed fear of Mr. B. whom he thought was "losing his mind." Mr. T. kept his light on that night to be sure Mr. B. did not come into his room in the dark and frighten him. This was considered to be a stressful situation for Mr. T. but was not associated with significant deviations in balance. On December 13, when Mr. T. and Mr. H. were reprimanded by a nurse for going to a candy vending machine, Mr. T. seemed furious and recounted the episode at length. His metabolic data, however, showed less striking changes than noted for Mr. H. on the same occasion and did not reach +2.0 S.D. which has arbitrarily been selected as "significant" for the present paper.

Summary of Stressful Events. During the eleven weeks in which this study was in progress there were 213 patient-days of balance data collected which could be used for the purposes of this report. During this time there were forty-eight patient-days on which

significant metabolic deviations occurred in association with stressful events. Thirty-eight of these were events which arose on the ward in association with ward routines and interpersonal relationships. Ten were related to people or events outside of the ward. These data are given in Table x.

Table xi gives an analysis of these situations in terms of their source in interpersonal relationships, ward treatments and routines, or other stresses. The importance of interpersonal relationships as a source of stress is evident from this table. Of forty-eight stressful situations associated with significant fluctuations, twenty-eight (58 per cent) were related to difficulties in interpersonal relationships on the ward.

SUMMARY

An attempt has been made to appraise the effects of naturally occurring stressful situations on certain metabolic indicators among a group of patients in the special social setting of the metabolic ward of a small research hospital. Variations in renal and fecal excretion were studied only in those patients who were on metabolic "balance" regimens and, except in special circumstances, on days when no complicating pharmacodynamic agents were being administered. The chemical data were kept separate from the personality studies of the individuals and judgments concerning stressful events and the prevailing atmosphere of the ward.

It soon became evident that the metabolic ward had the special characteristics of a well defined community with its own pressures, values, prestige points and taboos. Prominent among the ingredients of prestige seemed to be the seriousness of illness of the patient and the length of time he had been a patient on the metabolic ward. Prominent among the values of the ward were an emphasis on good manners and restraint. There was a penalty for those patients who went too far with levity on the one hand or showed a maudlin concern with illness and death on the other. The "ground rules" of behavior seemed to reflect the personality of the head nurse more than any other one specific factor.

Major metabolic changes in terms of urinary excretion of water, sodium, potassium, calcium, nitrogen and creatinine occurred repeatedly in situations of stress among the patients. Deviations in excretion of metabolites of greater than 2.0 S.D. occurred on sixty patient-days of a total of 213 for which data were available. There were several days considered to be stressful on which significant alterations in metabolic balance failed to occur. This failure correlated strikingly with the prevailing atmosphere of the ward. When the general atmosphere of the ward was disturbed 86 per cent of the presumed stressful events were accompanied by significant alterations in the balance data, while during relatively calm periods for the group as a whole only 48 per cent of presumably stressful episodes were accompanied by significant changes. Metabolic deviations of significant degree occurred on twelve of 146 (8 per cent) patient-days which had not been considered stressful.

It was of special interest that among those who were capable of reacting with metabolic alterations to stress was a man whose pituitary had been largely destroyed by a chromophobe adenoma and was subsequently removed surgically.

It could not be said that one patient was more reactive than another. The capacity for marked metabolic deviations in association with emotional responses was present in all, including the patient surgically hypophysectomized. Patterns of excretion suggestive of the activity of any single hormone were not clear-cut in association with any of the naturally-occurring stressful situations. ACTH and adrenal cortical hormones have variable effects upon excretion, depending upon the previous state of the patient; but they are usually associated with a potassium diuresis and sodium retention. In this study, potassium and sodium commonly showed deviations in the same direction, both being retained or lost simultaneously. The effects of other hormones are even more variable than that of ACTH. However, the impression gained was that the patterns of excretion were usually the resultant of multiple influences rather than the effect of any single hormonal agent.

Interpersonal difficulties were much the most common sources of stress to be associated with metabolic deviations. These accounted for twenty-eight of the forty-six stressful situations associated with such deviations. In general, they seemed to center in the most significant relationships. Interpersonal stresses arising between individuals without strong ties were less often associated with significant repercussions in the metabolic data. For example, the two most important relationships for Mr. H. were with Miss R. and Mr. T. All significant metabolic deviations related to interpersonal stresses occurred in association with situations arising in these two relationships. Although he had

difficulties in his dealings with Mrs. D., these were not associated with significant metabolic deviations.

Of special interest were the effects of anxiety among the nursing staff on the patients who were unaware of this disturbing situation. Every one of the group who were on metabolic balance at the time showed predominantly negative balances for the two-day period during which this disturbance persisted.

In conclusion, it is our opinion that this pilot study has demonstrated that the metabolic ward is not necessarily a "neutral environment" and that adequate interpretation of metabolic deviations in patients must include an appraisal of their life situation and emotional state at the time.

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Seminar on the Brain

Pathological Effects of Cerebral Anoxia*

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THE term "hypoxydosis" (Haymaker and Strughold [1]) includes all disturbances of biological oxidation resulting from decreased oxygenation of tissue. One form of hypoxydosis is anoxia, reduction of the intracellular oxygen supply below a critical level [2]. Enzyme deficiency hypoxydosis due to inhibition of intracellular respiratory enzyme systems, or to vitamin deficiency, is often called "histiotoxic anoxia." Nutritional deficiency hypoxydosis occurs in the absence of nutritive substrate, as in hypoglycemia [2].

The clinical manifestations of cerebral anoxia are apparent upon direct observation, and they may persist after cessation of an anoxemic episode. The outcome often is fatal.

The pathological effects of anoxia in general, and in the central nervous system in particular, are the expression of "vulnerability" [3]. Vulnerability differs from organ to organ and may present area differences within a single organ. "Revival time" [2] is the maximum time interval measured from the onset of anoxia after which complete restitution of function, usually measured by the electroencephalogram, is still possible. "Revival time" corresponds closely to "vulnerability." "Survival time" [26] is the time interval between onset of anoxia and cessation of function. "Survival time" and "vulnerability" are not identical.

Brown Séquard in 1858 was the first to discover differences in vulnerability of the cerebrum, medulla, spinal cord and peripheral nerves after transient interruption of the blood supply. This discovery was the basis of all future and more detailed studies.

The structural elements of the central nervous system are subject to anoxic damage in a fixed order of vulnerability: (1) the neuron, (2) oligodendroglia, (3) astroglia, (4) microglia, and (5) connective tissue structures [4,5].

Differences in areal vulnerability may be greater than the vulnerability of individual structural elements. After general anoxia, areas of cortical necrosis may be found adjacent to areas in which all structural elements of the cortex are fully preserved.

Cerebral anoxia may be general, as in cardiorespiratory arrest, or local, as in obstruction of a cerebral artery with subsequent encephalomalacia.

GENERALIZED CEREBRAL ANOXIA

The brain receives 700 to 1000 cu. cm. of blood per minute, 20 to 25 per cent of the output of the left ventricle [6]. The arteriovenous oxygen difference is greater in the cerebral circulation than in other organs. In man the consumption of oxygen by the brain is second only to that of the thyroid gland [7]. On acute reduction of the blood supply to somewhat below half the normal value the oxygen consumption remains constant while the arteriovenous oxygen difference increases. At a venous blood O_2 pressure of 19 mm. the oxygen consumption of the brain decreases. This level, determined by animal experiments, corresponds to the level at which alteration of cerebral function is observed in man. On further reduction of the oxygen consumption to 20 per cent of normal the electrical reactions are reduced to a minimum but can be fully restored after unlimited revival time—"Erhaltungsumsatz" (maintenance oxygen consumption). Below this level irreversible damage takes place. These data are based on the experimental work of Hirsch et al. [8,9].

The survival time and revival time of the central nervous system are short, amounting to minutes only. The actual measurements by different investigators using different methods are somewhat at variance. Survival times for different functions of the central nervous system in ischemia, based on animal experiments

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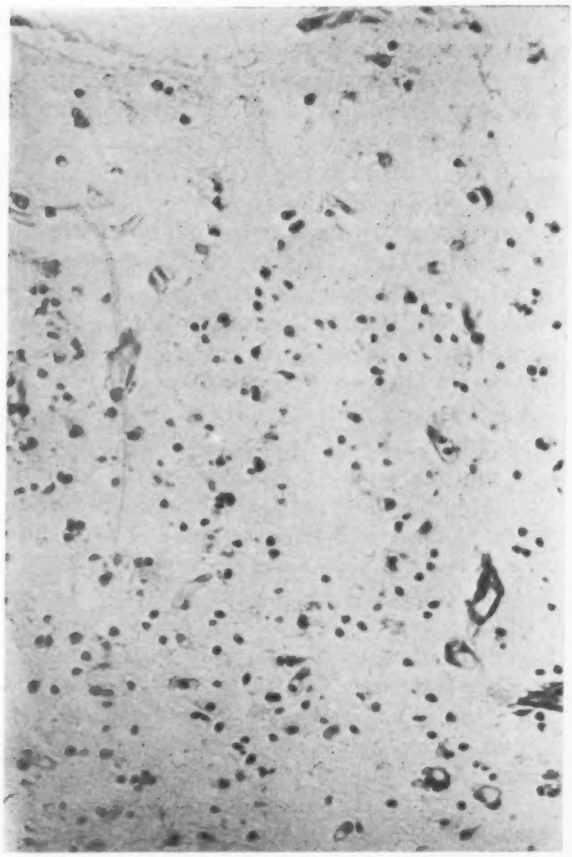

FIG. 1. Cortex, six days after cardiac arrest. Selective neuronal necrosis. Note dilated vessels, swelling of endothelial cells. Original magnification × 196.

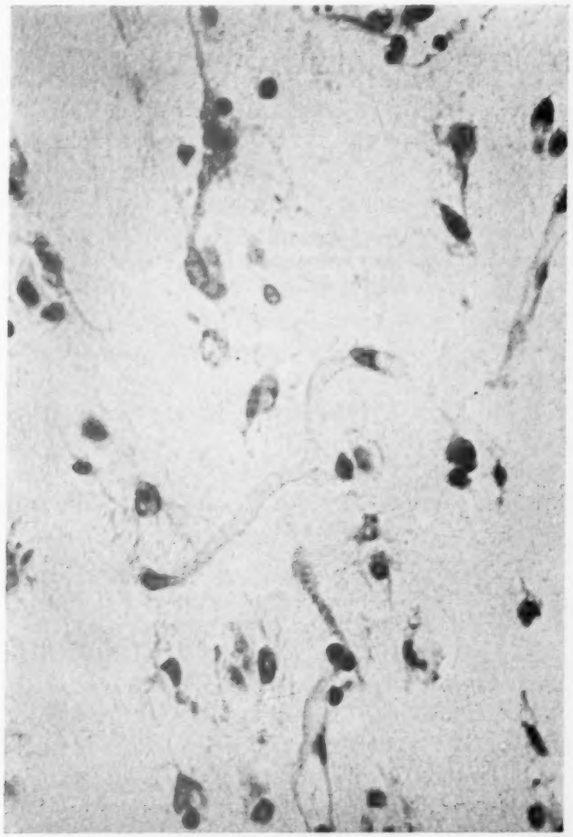

FIG. 2. Same as Figure 1. Activated astrocytes. Original magnification × 410.

primarily, are as follows: cortical center, five minutes; corneal and pupillar reflex, five to ten minutes; vasomotor and respiratory regulation, fifteen to thirty minutes [*10*]. Compared with the observed revival time in man of 100 seconds [*6*] to two minutes after cardiac arrest, the experimental figures are high. This difference is possibly accounted for by the fall in body temperature during the animal experiments and also by the residual circulation [*3*].

The morphological effects of anoxia vary from case to case, depending to some extent upon the manner of causation. The classification of anoxia is commonly based on pathogenesis, as in the following classification by Fog [*11*], which corresponds closely to that of Courville [*12*].

(1) Anoxic anoxia—reduced oxygen intake—e.g., respiratory arrest.

(2) Anemic anoxia—reduced transportation—e.g., acute or chronic anemia.

(3) Stagnant anoxia—reduced diffusion—e.g., cardiac arrest.

(4) Histiotoxic anoxia—reduced cell oxidation—e.g., cyanide poisoning.

Carbon monoxide anoxia is sometimes included in the group of anoxic anoxia, but by others in the group of anemic anoxia. Further, there is much overlapping in the types of anoxia, for example in respiratory arrest, which is often associated with a marked fall in blood pressure. Generalized acute anoxia of the nervous tissue due to various causes is usually complicated by local stagnant anoxia due to intracerebral circulatory disturbances elicited directly or indirectly by the generalized anoxia.

The pathological effects of anoxia on the nervous tissue are of two types: (1) Selective neuronal necrosis (Fig. 1); and (2) malacia [*12*]. Selective neuronal necrosis is observed when the anoxia is not severe enough to damage the astroglia. (Fig. 2.) It is essentially a nerve cell necrosis followed by glial repair. Encephalomalacia can occur only when anoxia is sufficiently severe to damage not only the neuron but also the astroglia [*4*]. The result is necrosis and liquefaction of the areas affected, eventually

leading to cyst formation. In rare instances liquefaction does not take place and the necrotic tissue remains *in situ* as a firm mass, "coagulation necrosis." Selective parenchymal necrosis is more common in generalized anoxia whereas malacia is commonly seen in localized ischemic anoxia.

The morphological changes of the neurons in selective parenchymal necrosis have been extensively studied but there is still considerable controversy as to the significance of the nerve cell lesions. Autolysis and absence of autolysis of the nerve cells contribute to the variation in the histological pictures. The prototype of the nerve cell lesion in selective parenchymal necrosis is "ischämische Zellerkrankung" (ischemic cell disease) [*4,5*]. It may appear as early as thirty minutes after the onset of anoxia. If a sufficient number of nerve cells are so affected, areas of selective necrosis of the grey matter stand out in the thionin-stained sections as pale patches, so called "Erbleichungen" (pale areas).

The various types of anoxia elicit distinct patterns of vulnerability but the differences are counterbalanced by the similarity of the basic mechanism and by secondary changes, such as local circulatory disturbances, resulting in local stagnant anoxia. Secondary circulatory disturbances and factors not yet clearly analyzed play an important role in the acute forms of anoxia [*4,5*].

Anoxic Anoxia. In this type of anoxia the oxygen intake is reduced while the blood circulation is maintained. Examples of this condition are: the anoxia associated with narcosis, carbon monoxide poisoning and chronic anoxia in cases of cardiac anomalies.

Scholz [*13*] described in detail the central nervous system findings in a case of Morbus caeruleus. He found a reduction in the number of nerve cells to about four-fifths of normal in the globus pallidus, corpus Luysi and dentate nucleus. The striatum and the inferior olive were similarly involved but to a lesser degree. The cell loss was diffuse, involving the entire nucleus and was symmetrical. The cerebral cortex, including the cornu ammonis, and the cerebellum, were not affected. The remaining nerve cells of the affected nuclei were atrophic. There was marked fibrillary gliosis in the affected nuclei while only mild gliosis was seen in the white matter of the cerebrum and cerebellum, without distinct fiber loss. Gliosis without noticeable nerve cell loss was also noted in the floor of the fourth ventricle.

Abbott and Courville [*14*] described selective pallidum necrosis without cortical alterations after nitrous oxide anesthesia complicated by respiratory arrest. Not uncommonly damage to the cerebellum and cerebral cortex may be associated with necrosis of the pallidum. The cortical lesions are both laminar and focal "Erbleichungen." Selective pallidum necrosis and malacia are constant findings in carbon monoxide poisoning, but here too cortical lesions, including the Ammon's horn, tend to occur [*15*]. Occasionally demyelinating lesions of the white matter are also seen.

Anemic Anoxia. In this form of anoxia oxygen transport is reduced. Plambeck [*16*] found no significant lesions in patients with chronic anemia with reduction of the hemoglobin to 16 per cent of normal. In some cases of secondary anemia pallidum lesions are conspicuous [*4,5*].

Stagnant Anoxia. Here arrest of the circulation is the causative mechanism. The prototype of this affection is cardiac arrest, and the condition has been reproduced experimentally by circulation arrest. The pattern of lesions in the experimental animal, in order of apparent vulnerability, is as follows: (1) cortex including the cornu ammonis; (2) Purkinje cell system of the cerebellar cortex (Fig. 3); (3) basal ganglia and medulla; (4) thalamus; and (5) pallidum, substantia nigra and corpus subthalamicum [*4,5*]. In the human brain after cardiac arrest the distribution of lesions is similar but the Purkinje cell layer of the cerebellum and the striatum are of about equal vulnerability [*4,5*].

Burne [*17*] stresses the importance of anoxic episodes during nitrous oxide anesthesia in dental practice. By survey he ascertained that in the United Kingdom about 500 cases occur every year in patients who did not regain consciousness immediately after nitrous oxide narcosis for dental extraction. He obtained detailed case histories in ninety-nine instances and lists fourteen fatal cases within two and a half years beginning October 1954. Some of these patients presented severe and occasionally persistent neurological signs after regaining consciousness. He described the postmortem findings in two cases of delayed death. In one case, fatal after thirty-four hours, lesions in the nature of ischemic necrosis were seen in the cerebral cortex, including the Ammon's horn in the striatum and cerebellum. In the second case, fatal after eight days, there was cellular degeneration in the lenticular nuclei

resembling that seen in carbon monoxide poisoning. He concluded that fainting in the upright position, with fall in blood pressure, is the cause of cerebral anoxia in these cases and stressed the importance of the horizontal position in avoiding this type of accident. The signs of syncope may be interpreted as effects of anesthesia.

Bedford [*18*] described dementia due to cerebral anoxia in elderly patients with vasomotor collapse during acute myocardial infarction, lobar pneumonia, bronchopneumonia or acute severe diarrhea. Occasionally hemiplegia and athetosis may be seen in cases of acute myocardial infarction without gross anatomical lesions in the central nervous system (personal observation). Such cases, like many others, are due to a combination of stagnant and anoxic anoxia.

Of particular interest is neonatal and perinatal anoxia. The importance of nitrous oxide narcosis of the mother for neonatal and perinatal anoxia has been analysed and stressed by Courville [*19*]. According to Courville a wide range of neurological disorders, from porencephaly to progressive demyelination, is probably or possibly related to neonatal anoxia. On statistical grounds Keith and Norvei [*20*] conclude that neonatal and perinatal anoxia, while an important cause of perinatal mortality, has no significant influence on the incidence of neurological disorders, at least during the first four years of life. Scholz [*5*] described two cases of neonatal anoxia (Geburtsasphyxia) characterized by symmetrical involvement of the pallidum, corpus Luys and Ammon's horn and related the lesions to perinatal anoxic anoxia.

Histiotoxic Anoxia (*Enzyme Deficiency Hypoxydosis*). In this category oxygen is available but the respiratory ferments of the nerve cells are blocked. The classic example is cyanide poisoning. Meyer [*21*] stressed the preponderance of selective pallidum necrosis and the vulnerability of the substantia nigra and Ammon's horn. Cortical lesions also occur. In the white matter, necrosis in the corpus callosum may be seen.

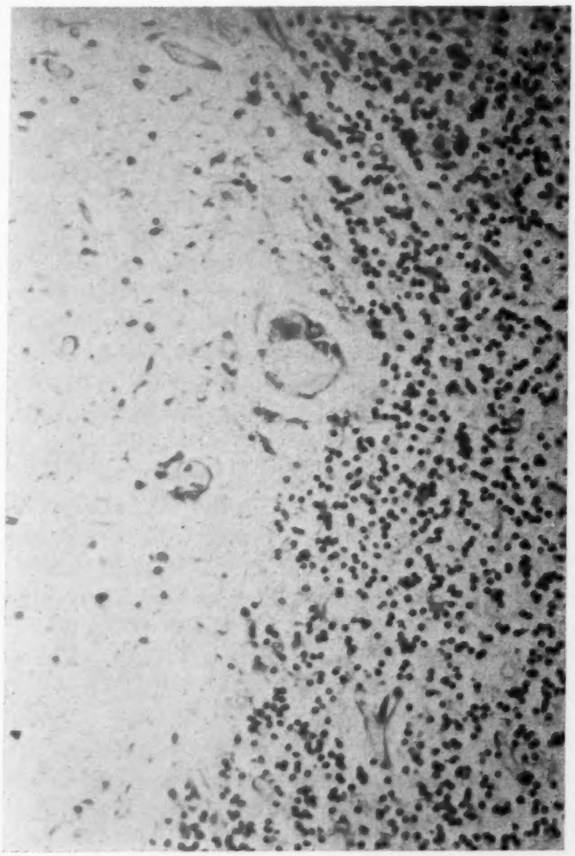

FIG. 3. Cerebellar cortex, same case as Figure 1. Selective neuronal necrosis of Purkinje cells. Note dilated vessels and swelling of endothelial cells. Original magnification × 196.

COMMENTS

It would thus appear that the pattern of anoxic damage in the central nervous system depends to some extent upon the type of anoxia. Special attention has been paid to the inverted pattern of vulnerability observed in anoxic anoxia as compared to stagnant anoxia. In anoxic anoxia, lesions of the pallidum, corpus Luys and dentate nucleus appear earlier and are more constant, while in stagnant anoxia cortical lesions predominate. On the other hand, Schmidt [*22*] in three cases of respiratory arrest (anoxic anoxia) and two cases of cardiac arrest (stagnant anoxia) found no significant difference in the pattern of vulnerability. Cortex and basal ganglia were about equally affected in both conditions. Nevertheless, distinct patterns of vulnerability, although possibly not constant in details, are maintained throughout. There is no case of cortical damage without pallidum damage in the anoxic anoxia group and there is no case of pallidum damage without cortical damage in the stagnant anoxia group.

There are differences in vulnerability not only of the grey matter of the cortex and basal ganglia but also within the cortex and within single areas of the cortex. The question arises as to the cause of this difference in apparent vulnerability. It has already been pointed out

that the structural elements of the central nervous system are subject to anoxic damage in a fixed order of vulnerability beginning with the neuron, followed by the neuroglia and connective tissue structures. If differences in areal vulnerability result in laminar cortical lesions the apparent vulnerability of laminas so affected is greater than the vulnerability of generally less sensitive structures, such as neuroglia.

The question of differences of vulnerability has been repeatedly discussed by two opposing schools. Thus C. and O. Vogt [*24*] developed the concept of "topistical pathoclisis." They explain the topistical variation in disease susceptibility by areal differences in structural and chemical composition. Spielmeyer [*23*] and his school reject the concept of topistical pathoclisis and explain differences in vulnerability by the "vasal factor"; local differences in vulnerability are explained by differences of vascular supply and vascular reactions.

In a careful analysis Scholz [*5*], the leading exponent of the Spielmeyer school, tried to ascertain the role of pathoclisis and of vasal factors, and also to reconcile some of the apparent incompatibilities. According to this author the pattern of vulnerability observed in chronic anoxic anoxia, with its predilection for the basal ganglia including the corpus Luys and the dentate nuclei, is the expression of a topistical pathoclisis. The focal lesions in acute anoxia, be it anoxic or stagnant, are the result of circulatory disturbances, the "vasal factor" of Spielmeyer [*24*]. Laminar cortical lesions and selective cell loss in the hippocampus and Purkinje cells of the cerebellum are explained by a background of topistical pathoclisis of the structures affected, but the eliciting factor is the circulatory disturbance associated with anoxia. In other words the circulatory disturbance affects the whole of the cerebellar cortex but only the topistical unit of the Purkinje cells, on the basis of its pathoclisis, is subject to degeneration. Apparent variations of the pattern of susceptibility in anoxic and stagnant anoxia are accounted for by the mixture of pathocline and vasal forms of damage. This interpretation goes a long way to reconcile opposing views of the two schools.

Accepting the role of the circulatory factor in explaining the effects of anoxia requires determination of the mechanism by which the vasal factor comes into play. Scholz [*5*], on the basis of experimental and human observations, stressed the importance of predominantly but not exclusively intracerebral local vascular spasm. This concept is based on the study of human and experimental animal brains subjected to anoxia, by means of variations of the Pickworth-Lepehne method. This method allows observation of the grade of filling and contraction of blood vessels.

Scholz [*5*] found marked vasoconstriction corresponding to areas of Erbleichung and laminar necrosis. This is, in his opinion, the cause of superimposed stagnant anoxia. In this interpretation vasospasm directly or indirectly elicited by anoxia explains the lesions not accounted for by topistical pathoclisis and in itself may bring out certain pathocline types of vulnerability, as in the Purkinje cell system of the cerebellum.

These observations can not be fully reconciled with experimental studies on this point. "Increase of arterial carbon dioxide causes profound dilation of cerebral arterioles with increase in the speed and volume of cerebral blood flow. Reduction of arterial CO_2 has the opposite effect. What is most significant, the effects are specific for cerebral vessels, the circulation of the extremities tending to decrease as that of the cerebrum increases" [*7*]. Vasoconstriction in the brain is slight if compared with other organs, the narrowing amounting only to 8 per cent of the diameter. Spasm of cerebral arteries and arterioles is only rarely observed.

Alternatively, the possibility that stagnant anoxia may be produced by stasis in the sense of Ricker [*25*] has been considered by Meyer [*21*] on the basis of his studies of experimental carbon monoxide poisoning and cyanide poisoning.

According to Cobb [*7*], the observed vasoconstrictor innervation of the cerebral vessels raises the question whether under abnormal conditions there may be vascular spasm sufficient to cause symptoms. There are no studies relating to the production of cerebral spasm in already anoxic brains. The possibility that the local intracerebral circulation may be regulated by the nervous elements of the supply area by liberation of carbon dioxide also has been considered [*41*].

In support of the pathoclisis concept Gruner [*27*] points out that besides lack of oxygen, a deficiency of other nutritive elements is of importance. The effects of such additional deficiencies are overshadowed by the effects of oxygen deprivation. Such nutritive deficiencies may affect the topography of subsequent

vascular accidents. By the use of isotopes Gruner [*27*] was able to show that the diffusion of ions into the nervous system varies according to the nature of the ions and in different regions. The variability of the diffusion factor should be taken into account when considering circulatory pathology.

Scholz [*4,5*] points out that the apparent vulnerability in anoxia is modified not only by the type of anoxia but also by the acuteness or chronicity of onset. This has been emphasized also by Schmidt [*22*]. Experimental evidence reveals that in acute anoxia, after complete exclusion of residual circulation in the decapitated head, the revival times of cortex, subcortical ganglia and mid-brain are equal whereas the medulla and cerebellar cortex have an increased revival time. After incomplete interruption of the blood supply, parts of the mid-brain and basal ganglia show a much longer survival time than the cortex [*3*]. The extended revival time of the medulla is partly explained by reflex excitability of medullary centers.

Vulnerability and revival time in the neonatal period require special consideration. Newborn mammals have a revival time greatly in excess of adults. Newborn rats survive fifty minutes in pure nitrogen whereas adults die after only three minutes. Viable infants have been removed fifteen to twenty minutes after the death of the mother [*2*].

The revival time in anoxic anoxia is longer than in stagnant (ischemic) anoxia. This has been attributed to the effect of the "Spuelfunktion" (flush effect) of the circulation by which toxic products, especially lactic acid, are removed. Experimental evidence in non-poikilotherm animals gives little indication of increase of survival time when the "Spuelfunktion" is maintained.

Absence of glucose increases the vulnerability to anoxia [*2*]. The cerebral lesions in hypoglycemia are interpreted as a form of hypoxydosis in which the absence of substrate results in nonutilization of oxygen, the nutritional deficiency hypoxydosis of Haymaker and Strughold [*1*].

With the introduction of hypothermia into general surgery, attention was directed to the effects of hypothermia on the central nervous system. It appears from the work of Rosomoff [*28,29*] that hypothermia results in a decrease of cerebral oxygen consumption; at 25°c. oxygen consumption is one-third of normal. Cerebral hypothermia thus serves as a safety factor against the consequences of prolonged or temporary interruption of major vascular channels.

Gaenshirt [*3*] stresses the importance of incomplete and time-limited revival. While equally vulnerable to complete circulatory arrest the cerebral cortex is more susceptible to partial arrest than the basal ganglia and the mid-brain. Of particular interest in this context is the observation that revival may be complete for a limited period; after fifty-five minutes of ischemia the proprioceptive reflexes of the cord reappear, only to disappear irreversibly. Time-limited revival is of clinical importance. The fate of a patient after anoxia is determined much earlier than would appear clinically [*3*].

Many questions remain unanswered. To name a few: To what extent are circulatory disturbances secondary to anoxia of the wall of cerebral vessels? What role is played by the loss of regulatory functions of the parenchyma which normally act upon the vascular tree? Is the vulnerability of the nervous parenchyma a direct effect of anoxia only or are vascular alterations with changed diffusion and nutritive disturbances significant?

LOCAL CEREBRAL ANOXIA

The basic mechanism in local cerebral anoxia is obstruction of a cerebral vessel or an equivalent situation. The result is local stagnant anoxia with malacia of the area supplied. The topographical relationship between vascular obstruction and malacia is usually explained by the concept of "endarteries," vessels without arterial, arteriolar or capillary anastomosis [*30*]. There is, however, general agreement that extensive and functionally significant anastomosis of meningeal vessels exists. Intracerebral arteriolar anastomosis is described by Pfeifer [*31*]. Cobb [*30*], who rejects the concept of endarteries in the central venous system, stresses the point that the capillary beds of individual cerebral arteries are closely linked with neighboring supply systems.

The pathological process of encephalomalacia has already been described in outline in the discussion of generalized cerebral anoxia. Encephalomalacia may be anemic or hemorrhagic. Hemorrhagic encephalomalacia is more common in the cortex than in the white matter. The hemorrhagic character of such lesions has been ascribed to residual circulation and venous reflux. According to Cobb [*30*] the hemorrhagic phase may precede the necrosis, and this applies

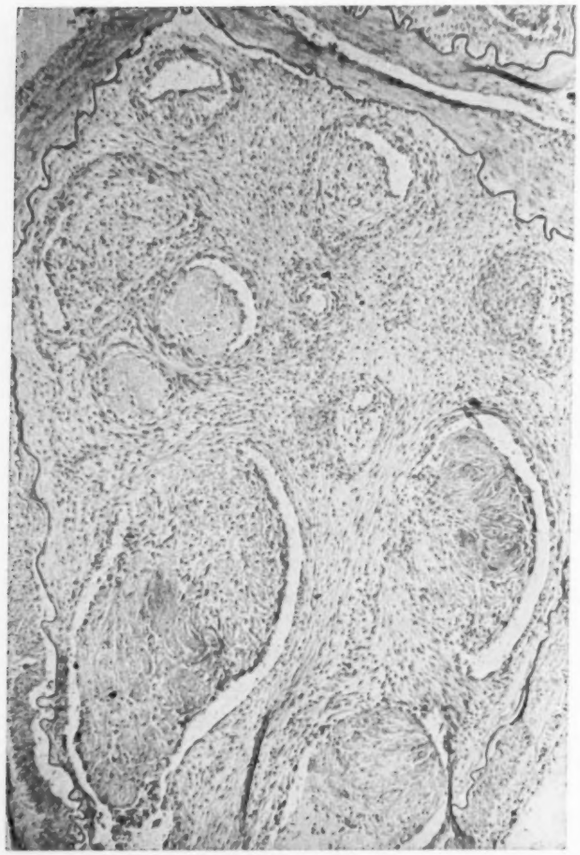

FIG. 4. Middle cerebral artery, secondary thrombosis of vessels within recanalized thrombus. Original magnification × 58.

also to the emigration of polymorphonuclears. Both phenomena could be the effect of red and white cell stasis preceding complete circulatory arrest.

The area of local anoxia and encephalomalacia may be as large as the supply area of the artery occluded [*32*] but is usually smaller. The following factors modify the anoxic effects of arterial occlusion: (1) Mode of occlusion; (2) variations in systemic blood pressure; (3) the condition of the vascular tree; (4) the extent of effective meningeal and intracerebral anastomosis; (5) recanalization of occluded vessels; and (6) alterations of body temperature, hypothermia.

Mode of Occlusion. Slowly developing thrombotic lesions produce less conspicuous clinical syndromes and smaller areas of encephalomalacia than do identically situated embolic lesions.

Variations in Systemic Blood Pressure. Blood pressure variations are particularly significant in the causation of carotid and basilar artery insufficiency syndromes. Partial or complete thrombosis of the carotid, usually beginning at the site of the bifurcation, may be oligosymptomatic unless complicated by embolism from the thrombus [*33*]. Transient insufficiency syndromes occurring in subjects so affected correspond to episodes of fall in systemic blood pressure [*34*]. Similar considerations apply to basilar artery insufficiency syndromes.

Conditions of the Vascular Tree. In young persons with vascular obstruction encephalomalacia is less extensive than in the aged with comparable vascular lesions. This indicates a greater adaptability of the vascular tree with better functioning alternative pathways.

Extent of Meningeal and Intracerebral Anastomosis. The importance of meningeal anastomosis between different supply areas, within supply areas, and across the midline has been stressed by Van der Eeken and Adams [*35*] (see also Lehrer [*36*]). This type of anastomosis may compensate for the effects of obstruction to a great extent. In the case of anastomosis over the midline, usually seen between the supply areas of the two anterior cerebral arteries, this may result in a paradoxical absence of symptoms or in the development of bilateral symptoms after obstruction of one anterior cerebral artery. Intracerebral anastomosis is less easily established. In cases of basilar artery obstruction the areas of infarction in the brain stem and cerebellum are smaller than expected on the basis of the supply pattern.

Recanalization of Occluded Vessels. Attention has been drawn to the occurrence of recanalization of meningeal and intracerebral vessels (Krainer [*37*]). In one personal observation, a patient with bilateral middle cerebral artery obstruction, two areas of recanalized thrombosis were found in the left middle cerebral artery. The thrombosis on the right side was not recanalized. The distal thrombosis in the left middle cerebral artery presented evidence of secondary thrombosis within newly formed vascular channels. (Fig. 4.) Corresponding with the findings at necropsy, the patient had two transient episodes and one terminal exacerbation of his symptoms. This case indicates that recanalization after arterial obstruction may result in restitution of the original supply channel and that secondary thrombosis may accentuate the clinicopathologic syndrome. It is also of interest in this case that the extent of the encephalo-

malacia was smaller than the area of supply, and also patchy, with relative well preserved areas between areas of softening.

Hypothermia. On the basis of animal experiments in dogs Rosomoff [*28*] listed the following effects of hypothermia: (1) a decrease in blood flow, (2) a corresponding reduction in cerebral metabolism, (3) an induced and compensated hypotension, (4) an increase in cerebral vascular resistance, (5) a decrease in brain volume, and (6) a diminution in intracranial pressure and venous pressure. Starting from the observation that interruption of the middle cerebral artery in the normothermic dog produces an area of significant infarction proportional to the degree and rapidity of occlusion [*38*], Rosomoff found that the effects of middle cerebral artery interruption under hypothermia were significantly reduced when compared with normothermic dogs similarly treated. He found further that the effects of interruption of the middle cerebral artery were reduced to a minimum if hypothermia was induced within fifteen minutes after operation and maintained for ninety minutes. He concluded that hypothermia may prove to be a valuable aid in alleviating and preventing the deleterious effects of prolonged or temporary interruption of major vascular channels. In his opinion the reduced metabolic requirements of the central nervous system during hypothermia make possible the establishment of an effective collateral circulation before significant anoxic damage occurs. Rosomoff also noted an inverted blood flow from the rami perforantes after resection of the trunk of the middle cerebral artery. This is evidence of effective intracerebral anastomosis.

The effects of arterial obstruction and anoxia are not always seen in the supply areas of the vessel affected but may be confined to the border zone between two supply areas [*32,39*]. The effects of venous obstruction are more variable. Alterations of the venous blood flow associated with birth trauma are of pathogenetic significance [*40*].

The occurrence of transient insufficiency syndromes, as well as of functional restitution after recanalization of an occluded artery necessitates the assumption that nervous tissue may subsist in an intermediate state not constituting necrosis and may subsequently resume functional activity. This hypothetic stage of "suspended animation" could well correspond to the experimental observation [*8*] that the electric activity of the cat brain reduced to a minimum at "maintenance oxygen consumption" (Erhaltungsumsatz) of about 20 per cent of normal may fully recover upon resumption of a normal blood supply, with unlimited "revival time."

Discussion of the mechanism by which transient insufficiency syndromes are elicited is still in flux. The concept of "vascular spasm," which led to unsuccessful attempts at cerebral vasodilation, has been supplanted by the concept of non-spastic circulatory insufficiency to be attacked by maintenance of blood pressure levels and increasing the oxygen supply.

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Clinico-pathologic Conference

Recurrent Bloody Pericardial Effusion

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine, and by Junior and Senior Medical Students. It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students from the Senior class rather than by members of the faculty.

A FIFTEEN year old white school girl, K. M., entered Barnes Hospital on October 27, 1957 with the complaints of increasing swelling of the right arm, face and eyes associated with nausea and vomiting of three days' duration. She died two days later.

Her first admission to Barnes Hospital was from September 27, 1957 to October 24, 1957. Three weeks prior to this admission, the patient's father had had "flu-like" symptoms. One week later the patient had had rhinorrhea associated with cough and a temperature of 101°F. She did not have a sore throat. She had remained home from school for a day, and had experienced unusual fatigue on the two subsequent days. The patient was given eight capsules of aureomycin® during the next two days. Eight days prior to this admission, because of tiredness and swelling of her eyes and ankles she had consulted her physician and had been admitted to a local hospital for five days. Although afebrile, she had received penicillin and streptomycin intramuscularly for four days. The ankle swelling had rapidly disappeared after she had been fed a low salt diet and the periorbital edema had persisted only in the mornings.

At home the patient had remained in bed, and had received aspirin, phenacetin and caffeine. There was slight dyspnea following exertion, but no orthopnea. Nocturia (once per night) was noted. The day prior to admission, the patient's physician informed her family that cardiac enlargement and possibly effusion had been detected on roentgenograms taken during her hospitalization, and the patient was referred to Barnes Hospital.

A hemangioma was present on the shoulder at birth. As an infant the patient had bronchopneumonia. She had had scarlatina, measles, mumps and varicella. She had experienced a "bad reaction" to typhoid vaccine. The family history and system review were within normal limits.

Physical examination showed a temperature of 37.5°C.; pulse, 120; respirations, 25; and blood pressure, 120/90 mm. Hg, bilaterally. The patient was a well nourished, well developed young girl in no acute distress. The skin was slightly pale. There were no palpable lymph nodes. Periorbital edema was present. The optic fundi were normal. The tonsils were enlarged, but not infected. The thorax was symmetrical. There was questionable dullness with decreased vesicular breath sounds at both lung bases. Rales were not present. The cardiac rhythm was regular. The point of maximal impulse was imperceptible. The left border of cardiac dullness was outside the mid-clavicular line. The second pulmonic sound was equal in intensity to the second aortic sound. A soft (grade 2) blowing systolic murmur was audible at the apex, along the left sternal border, and with decreased intensity at the base and in the left axilla. The abdomen was firm to palpation. The liver was questionably palpable 4 cm. below the right costal margin, with dullness in this area. The spleen was not felt. No abdominal tenderness or masses were noted. The peripheral pulses were palpable and equal. No cyanosis, edema or clubbing were present. The examination was otherwise normal.

Laboratory data revealed a hemoglobin level of 13.1 gm. per 100 ml. and a white blood cell count of 7,000 per cu. mm. The differential count showed 2 eosinophils, 2 bands, 70 polymorphonuclear leukocytes, 25 lymphocytes and

1 monocyte. The urine specific gravity was 1.010; reaction, 7.5; protein and sugar, negative. Only epithelial cells and an occasional leukocyte were found in the urinary sediment. The stool was negative to the guaiac reaction. The cardiolipin test for syphilis was negative. The non-protein nitrogen was 17 mg. per 100 ml.; fasting blood sugar, 84 mg. per 100 ml.; total protein, 6.9 gm. per 100 ml. with albumin/globulin 4.2/2.7, creatinine, 0.9 mg. per 100 ml.; and the protein bound iodine, 5.1 μg. per 100 ml. The erythrocyte sedimentation rate was 20 mm. (Wintrobe tube). Two preparations for L.E. cells were negative. The C-reactive protein was 2 plus, and the antistreptolysin O titer was less than 25 units. The cephalin-cholesterol flocculation test was negative and the thymol turbidity, 1.2 units. Heterophil and cold agglutinations were negative. The venous pressure was 265 mm. of saline and the circulation time (decholin®) was sixteen seconds. Fluoroscopic examination of the chest showed the cardiac pulsations to be markedly reduced. Kymography confirmed this observation. Roentgenograms revealed cardiac enlargement, with a silhouette suggestive of pericardial effusion, changes of pulmonary edema with congestion, and pleural effusions. A single frontal view of the chest suggested the possibility of left ventricular aneurysm. An electrocardiogram showed sinus tachycardia, with a rate of 100. The P-R interval was 0.14 second, the QRS duration was 0.06 second. Because of low voltage in the limb leads and T wave abnormalities, the record was interpreted as being compatible with pericarditis. Throat culture grew Neisserian organisms and non-hemolytic streptococci. The second strength P.P.D. and the histoplasmin skin tests were negative.

While in the hospital, the patient was treated with bedrest and salt was restricted. During the first seven days, there was a loss of 9 pounds in weight. The administration of a mercurial diuretic resulted in an additional loss of 4 pounds in twenty-four hours, but the second dose of the mercurial six days later produced no further diuresis. The blood pressure ranged from 100/80 to 130/90 mm. Hg and pulse from 90 to 130, remaining usually in the range of 100 to 110. Daily urinalyses during the first week showed a maximum specific gravity of 1.019, an occasional white blood cell, but no red blood cells or protein.

On the twelfth hospital day, a pericardiocentesis was performed. Two hundred twenty ml. of serosanguinous, chocolate colored fluid was removed, and 80 ml. of air was instilled into the pericardium. The fluid cultured for bacteria, acid-fast bacilli and fungi failed to show any growth. Roentgenograms at this time demonstrated a hydropneumopericardium, with a suggestion of loculation. The possibility of infiltration in the lower right and possibly the middle right lobes of the lung was suggested on the lateral film, but not confirmed by further projections. Twenty-four hours later, the patient's temperature rose to 38°C. (per os). A pericardial friction rub was audible then and for the subsequent seventy-two hours. A blood culture obtained at this time remained sterile for twenty-one days. Four days later, the temperature rose to 38.4°C.; blood culture was again obtained and remained sterile. A chest film showed no change from the admission film except for accumulation of fluid in the right cardiophrenic sulcus, and perhaps increase in the density and extent of infiltrative process arising at the right hilum.

By the following day, the patient's temperature had returned to normal. During the first eighteen days of hospitalization, the electrocardiogram showed minor variations in the appearance of the T waves. On the eighteenth hospital day, a second pericardiocentesis was performed, with the removal of 500 ml. of bloody fluid. The fluid had a specific gravity of 1.022, a total cell count of 150, 80 per cent of the cells were lymphocytes. The protein concentration was 5.3 gm. per 100 ml. No organisms were seen on Gram and acid-fast stains of this fluid. Cultures placed on a blood agar plate were sterile, but a few colonies of coagulase positive yellow staphylococci were isolated from a thioglycolate broth culture. Cultures for acid-fast bacilli and fungi were sterile. Inoculation of a guinea pig with this fluid failed to produce tuberculous lesions in the animal. Cytological studies of the fluid were reported as showing "atypical cytology but no evidence of malignancy." Pathologic sections prepared after fixation in formalin showed many lymphocytes, in addition to many mesothelial cells, and rare neutrophils. The lymphocytes were larger than normal, and showed moderate variation in both size and shape. A definitive diagnosis could not be made.

The patient remained in the hospital an additional ten days. The hemoglobin, white

blood cell count and differential remained normal. The erythrocyte sedimentation rate was 12 mm. per hour. A repeat antistreptolysin O titer was less than 25 units. The patient lost 3 pounds in weight. A single spike in temperature to 38°C. occurred on the twenty-second day. Roentgenograms of the chest showed no change from those obtained prior to the second pericardiocentesis. It was decided to give the patient a short vacation from the hospital. An electrocardiogram on the day of discharge showed a greater degree of inversion in the T waves. No medication was given to the patient.

The second admission to Barnes Hospital was from October 27, 1957 to October 29, 1957. After returning home, the patient had been unable to eat because of nausea and vomiting. She had been unable to sleep at night. On the morning of admission, she had noted pain and swelling of the right arm and right side of the neck as well as an increase in facial and periorbital edema. Slight discoloration of the right arm had also been noted.

Physical examination showed the following: temperature, 37.6°C.; pulse, 100; respirations, 20; blood pressure, 140/80 mm. Hg. The patient's weight had not increased. The changes present since her discharge included marked swelling of the face, periorbital areas and the right side of the neck. The edema was soft but did not pit with pressure. The neck veins were distended. There were rales scattered throughout the lung fields; dullness and decreased breath sounds were noted in the right posterior lung field. The pulse was paradoxical. Cardiac dullness extended to the anterior axillary line. A grade 3 systolic murmur was heard over the entire precordium, and posteriorly to the left of the fourth dorsal vertebra. The liver was palpable 7 cm. below the right costal margin. The right arm was cyanotic. There was no pedal edema.

Laboratory data were as follows: the hemoglobin was 14.5 gm. per 100 ml.; the white blood cell count, 14,150 per cu. mm. with 1 eosinophil, 81 polymorphonuclear leukocytes, 17 lymphocytes and 1 monocyte. The urinalysis showed a specific gravity of 1.025, but was otherwise within normal limits. The venous pressure had risen to 325 mm. saline. The circulation time was further prolonged to twenty seconds (decholin). The electrocardiogram was unchanged. A chest roentgenogram showed an increase in the pericardial effusion, greater widening of the mediastinum, and increase in the bilateral pleural effusions.

The patient's temperature rose to 38.3°C. on the second hospital day. On the third hospital day, an exploratory thoracotomy was performed. The tense, swollen, pericardial sac was opened and approximately 1 L. of bloody fluid was removed. There was some thickening of the pericardium, but no gross tumor implants. The pericardium was biopsied, and a pericardiostomy was performed. Culture of the pericardial fluid grew two colonies of yellow staphylococci, which were thought to be contaminants. No acid-fast bacilli were seen on a direct smear. Cytological examination showed atypical cytology but no evidence of malignancy. Histological examination of the pericardium showed infiltration of lymphocytes about the small blood vessels. The pericardial fluid contained many lymphocytes, which varied somewhat in size and shape. Erythrocytes and mesothelial cells were also present. A definitive diagnosis could not be made.

After one hour in the recovery room, hypotension developed with a systolic blood pressure of 90 mm. Hg by palpation. A tachycardia of 160 to 170 developed; tachypnea and cyanosis were apparent. An electrocardiogram showed sinus tachycardia, with the rate of 160 per minute. Changes in the limb leads were suggestive of acute cor pulmonale. Lanatoside C was administered intravenously and morphine hypodermically. At this time, the hemoglobin was 13.9 gm. per 100 ml.; the red blood cell count, 5.38 million per cu. mm.; the hematocrit, 48 per cent; and the white blood cell count, 27,100 per cu. mm. In the ensuing two hours, the patient's face and neck became more edematous, the neck veins became more distended, and cyanosis became more marked. The patient's blood pressure could no longer be obtained and did not respond to norepinephrine administered intravenously. The patient died six hours after she had entered the recovery room.

CLINICAL DISCUSSION

DR. SOL SHERRY: This conference deals with the problem of a recurrent bloody pericardial effusion in a fifteen year old white girl who exhibited a progressively downhill course and died six weeks after the onset of her illness. Mr. Gottchalk will present the roentgenograms.

MR. ALEX GOTTCHALK: The roentgenograms

taken on the first admission showed a grossly enlarged cardiac silhouette and pleural effusion. Films of the stomach and duodenal bulb appeared within normal limits. In the chest examination taken four days following admission, the trachea was in normal position; the cardiac silhouette demonstrated a picture typical of pericardial effusion with a loss of identity of the pulmonary artery and the left atrial appendage. In the lateral projection, the anterior mediastinum appeared darker than usually seen and considerably more dense. This unusual density might have been due to effusion but the possibility of a mass in this area cannot be excluded. Kymograms revealed markedly diminished ventricular pulsations, consistent with a pericardial effusion. In addition, the aortic pulsation was also diminished suggesting a lowering of the stroke volume. In films taken after the pericardial tap and instillation of air, the heart appeared to be normal in size, or perhaps smaller than normal. There was an infiltrate in the upper right lobe which appeared to be of infectious origin, although tuberculosis appeared doubtful. In summary, we have evidence of a pericardial effusion with rapid reaccumulation of fluid following the tap, bilateral pleural effusions, a pneumonitis of the upper right lobe and the possibility of an anterior mediastinal mass.

DR. SHERRY: Mr. Catanzaro, will you interpret the electrocardiograms?

MR. RONALD CATANZARO: The first electrocardiogram taken on September 28, at the time of the first admission, revealed a sinus tachycardia of 100 per minute, a QRS duration of .06 second, flattening and inversion of T waves in leads I, AVR, AVL, and all the V leads. Low voltage was noted in all leads. The tracing is consistent and suggestive of a pericardial effusion. Absence of Q waves militates against a myocardial infarction. The next electrocardiographic record was taken on October 15 and showed very little change except for a slight diminution in the size of the R waves probably indicative of a greater pericardial effusion. On October 24, after the pericardiocentesis, the R waves appeared to increase in size. On the last record, taken October 29, right axis deviation was very striking, suggesting an acute cor pulmonale, perhaps secondary to pulmonary embolization.

DR. SHERRY: Mr. Wilkinson, would you review the cytological examinations on the pericardial fluids and discuss the pericardial biopsy?

MR. ROBERT WILKINSON: The cell blocks of the pericardial fluids showed fresh red cells and a layer of white cells, mostly lymphocytes. These lymphocytes were larger than normal and varied moderately in size and shape. There were a few rosettes of mesothelial cells compatible with any non-specific serous surface irritation. Occasionally mitoses were seen in these large cells. The biopsy specimen of the pericardial sac showed perivascular lymphocytic infiltrations. These lymphocytes were similar to those found in the pericardial fluid. No necrosis of vessels or vessel walls could be seen. These findings must be considered compatible with a lymphomatous involvement but are certainly not diagnostic. Other conditions could present a somewhat similar picture.

DR. SHERRY: One of the outstanding features in this case was the presence of bloody pericardial fluid. Mr. Porterfield, will you name those diseases which may produce this type of effusion.

MR. JOHN PORTERFIELD: Almost any type of pericardial effusion may be hemorrhagic. Some of the more common causes are: rheumatic fever, tuberculosis, trauma, myocardial infarction, acute non-specific pericarditis or benign idiopathic pericarditis, uremia, disseminated lupus, and finally, malignant neoplasm. There are a few more rare causes of hemorrhagic effusion which do not merit more attention than to mention them. There are parasitic invasion of the pericardium, syphilitic gumma, and polyarteritis nodosa.

DR. SHERRY: May a hemorrhagic effusion be due to a myocardial infarction?

MR. PORTERFIELD: Although pericarditis is fairly common in myocardial infarction, and friction rubs are audible in approximately one-fifth of the cases, pericardial effusions are relatively infrequent. However, a clinical syndrome similar to benign idiopathic pericarditis may complicate the course of acute myocardial infarction. A hemorrhagic effusion following an acute myocardial infarction would be very rare providing we exclude the hemopericardium which follows cardiac rupture.

DR. SHERRY: Of the diagnostic possibilities mentioned, which do you believe can be excluded?

MR. PORTERFIELD: There is no reason to suspect trauma, and we can exclude myo-

cardial infarction in view of the patient's age, absence of pain, and lack of history. Since renal function was adequate, uremia may also be ruled out. Rheumatic fever need not be seriously considered since there is nothing in the history, physical or laboratory findings to support this diagnosis.

DR. SHERRY: Mr. Calvert, would you agree that we can exclude rheumatic fever from further consideration?

MR. JOHN RANDOLPH CALVERT: Yes. The consistently low antistreptolysin O titer, the absence of signs or symptoms of rheumatic fever, the fairly low C-reactive protein, the low sedimentation rate, and the absence of subcutaneous nodules, which are found more often in rheumatic pericarditis than in other kinds of rheumatic fever, make the diagnosis of rheumatic fever untenable.

DR. SHERRY: May we see isolated pericarditis in rheumatic fever?

MR. CALVERT: Although pericarditis is an extremely frequent and characteristic pathological lesion in rheumatic disease of the heart, occurring in almost 100 per cent of the cases on microscopic examination, clinical pericarditis is diagnosed much less frequently, or only in approximately 5 to 10 per cent of cases. When it is diagnosed, the heart disease is usually more serious. Slight degrees of effusion are more often associated with acute rheumatic pericarditis, than large effusions. When pericarditis occurs clinically, it is almost always associated with evidences of myocarditis and endocarditis, since rheumatic involvement of the heart is best considered as a pancarditis.

DR. SHERRY: Mr. Broadwater, would you discuss the possibility of tuberculous pericarditis?

MR. JOHN BROADWATER: This patient had no constitutional symptoms, no night sweats, no history of fever, and no history of exposure to tuberculosis. She had a negative skin test, and cultures of the pericardial fluid were consistently negative for acid-fast organisms. These considerations represent strong evidence against the diagnosis of tuberculosis. However, there is no doubt that the fluid in tuberculous pericarditis may show a lymphocytic predominance and may be bloody in nature. As a matter of fact, excluding trauma, tuberculosis and neoplasia are the commonest causes of hemorrhagic pericarditis and of cardiac tamponade.

DR. SHERRY: Is tuberculous pericarditis more often seen in young or in old people?

MR. BROADWATER: It occurs more frequently after the age of forty, although it may occur in young adults or children. There is a predilection for males, and it occurs more frequently among Negroes.

DR. SHERRY: Is it not true that a large number of patients with tuberculous pericarditis come to autopsy without ever having had positive pericardial fluid cultures?

MR. BROADWATER: Yes, approximately one-third to one-half of the cases require postmortem confirmation because of repeatedly negative cultures.

DR. SHERRY: Mrs. Harkness, do you have a comment?

MRS. MARY HARKNESS: I read of an interesting case in which a patient with tuberculous pericarditis had a positive skin test late in the course of the disease. Early, the skin and all cultural studies had been negative.

DR. SHERRY: Although we cannot exclude tuberculous pericarditis, I have the impression that none of you favors it as your primary diagnosis. Mr. Mantini, did you give any consideration to the entity of non-specific or benign idiopathic pericarditis?

MR. EMIL MANTINI: Yes, that diagnosis must be considered. However, it is a disease primarily occurring in males which is usually characterized by considerable chest pain, fever and leukocytosis. The disease is usually benign. Our patient did not have the findings commonly seen in idiopathic pericarditis. In addition, she had swelling of the right arm and the right side of the face, findings which would make the diagnosis somewhat difficult to accept.

DR. SHERRY: Yes, clinically there is little to support the diagnosis. Although idiopathic pericarditis is usually a benign disease, in isolated instances it may be fatal. Can you tell us something about the nature of the pericardial fluid in benign idiopathic pericarditis?

MR. MANTINI: It is usually serous at the onset of the disease and the cytology may be variable. However, later in the course particularly after the tenth day, the fluid may become bloody, and lymphocytes predominate, similar to the findings in this patient's pericardial fluid.

DR. SHERRY: Mr. Catanzaro, would you comment on the nature of pain in pericarditis?

MR. CATANZARO: Pain in pericarditis may be sharp and severe, or dull and vague. It usually appears over the precordium, but may radiate in a similar fashion to the pain of angina and

may be readily confused with the latter. The pain is often aggravated by deep inspiration, motion of the chest, or cough, suggesting involvement of the pleura. It may also be intensified by swallowing, or the recumbent position. As a matter of fact, patients with severe pericarditis usually are most comfortable sitting up and leaning forward. Actually some patients assume a knee-chest position.

The pathogenesis of pain in pericarditis may be quite complex. It should be remembered that the visceral pericardium is devoid of pain fibers. The lower part of the parietal pericardium is supplied by the phrenic nerve, which may account for pain referred to the shoulder or neck. In addition pericardial effusions may produce a dull oppressive pain by distending the entire pericardial sac and stimulating the pain sensitive fibers of the parietal pericardium. Finally pericarditis is often associated with a contiguous pleuritis, and it is the latter which most often accounts for the sharp pain seen in some cases.

DR. SHERRY: Mr. Gass, the diagnosis of systemic lupus has been mentioned as a possibility in our patient. Do you believe that diagnosis deserves serious consideration?

MR. MICHAEL GASS: Disseminated lupus is not a likely possibility. Although systemic lupus certainly occurs in young females, there is very little to support the diagnosis. When pericarditis occurs in lupus, the fluid is of much lesser amount than described in this case, and there is often a generalized polyserositis, not simply an involvement of the serous membranes of the heart.

DR. SHERRY: I could find one case report of a large, bloody pericardial effusion in lupus. Were any of you able to find additional cases?

MR. PORTERFIELD: I found seven cases of lupus with large effusions but in addition to the effusion, all the patients had prominent constitutional symptoms and a pronounced nephritis.

DR. SHERRY: Except for neoplastic disease, you have excluded all the common causes of a recurrent hemorrhagic pericardial effusion. Mr. Gass, is neoplastic disease your choice?

MR. GASS: Certainly the entire course of this girl's disease is compatible with a malignant neoplasm in the mediastinum with chronic cardiac tamponade and a superior vena caval syndrome. The onset of symptoms, with an upper respiratory-like syndrome, at first glance, did not seem to be compatible with the diagnosis of malignant disease. However, the reports in the literature indicate that this is not an uncommon finding in pericarditis associated with neoplasm. It is disturbing that the diagnosis was not established at surgery. However, the exploration was limited.

DR. SHERRY: Mr. Gottschalk, what types of neoplasms of the heart and pericardium may one encounter?

MR. GOTTSCHALK: Of the primary neoplasms, three-quarters are benign, and consist almost exclusively of myxomas and rhabdomyomas. The myxomas arise from the endothelium, are usually in the left auricle, and may occlude the mitral orifice giving rise to a clinical picture similar to that seen with an obstructing thrombus. The rhabdomyomas are less frequent than the myxomas, arise in the myocardium, are often multiple, and may be associated with conduction defects and arrhythmias. For some unknown reason, they may be found in association with tuberous sclerosis, and adenoma sebaceum of the skin. Primary malignant tumors are usually sarcomas arising from the endothelium but occasionally from the pericardium. They are usually on the right side in the vicinity of the right auricle. They may be hemorrhagic, and may produce a clinical picture indistinguishable from the one presented by our patient.

Secondary neoplastic diseases of the heart are more often carcinomas than sarcomas. They may involve the endocardium, myocardium or pericardium. These, too, are more often found on the right side of the heart than the left. Metastatic disease of the heart most often arises from primary tumors of the lung, breast or malignant melanomas. A variety of other tumors may metastasize to the heart, but this is usually a late event and associated with generalized carcinomastosis. Finally lymphomas frequently involve the heart either by primary invasion or by secondary metastases.

DR. SHERRY: Mr. Broadwater, would you comment on the incidence of primary neoplasms of the heart?

MR. BROADWATER: Primary neoplasms of the heart are rare. The incidence is only 0.04 per cent as compared to an incidence of 0.5 to 1.0 per cent for secondary neoplasms. The ratio of secondary to primary is roughly 30:1. In 5 to 10 per cent of patients with neoplastic disease there will be evidence of invasion of the heart and pericardium at autopsy.

DR. SHERRY: You have stated that secondary

neoplasms occur thirty times as frequently as primary tumors. What is the mode of spread to the heart?

MR. BROADWATER: Most of the secondary neoplasms reach the heart by involving the tracheobroncheal lymph nodes. They then spread by retrograde extension to either the myocardium or the pericardium. The second most common mode of extension is directly from the lung or mediastinum. Finally, hematogenous spread may also seed the heart.

DR. SHERRY: Now if one takes a person with a specific neoplastic disease, what would be the incidence of cardiac or pericardial metastases?

MR. BROADWATER: Studies on this subject relate to patients dying of carcinomatosis. The highest frequency of involvement would be from malignant melanomas in which an incidence as high as 85 per cent has been reported. Carcinomas of the breast and lung involve the heart in roughly 60 per cent of the cases. Lymphomas, which are of considerable interest in relation to our case, have about the following incidence: Hodgkin's disease, 30 per cent and lymphosarcoma, roughly 44 per cent.

DR. SHERRY: What are the usual clinical manifestations of malignant disease of the heart?

MR. BROADWATER: Most of them produce no symptoms. Sometimes with metastatic tumors of the heart, the cardiac findings are obscured by other evidences of carcinomatosis. However, on occasion, tumors of the heart produce signs and symptoms related to obstruction of blood flow, interference with normal electrical conduction, or extensive involvement of the myocardium or pericardium. Distinctive clinical syndromes such as recurrent bloody effusions with evidence of chronic cardiac tamponade and a superior caval syndrome, as exists in our patient, strongly suggest malignancy and have been emphasized in the literature, but are relatively uncommon. Most often pericardial effusions are small and the pericardial sac may be obliterated by extensive fibrous adhesions.

DR. SHERRY: To summarize, you believe this patient has neoplastic disease of the heart, and on a statistical basis, the neoplasm would more likely be metastatic than primary. Would you be willing to make a specific diagnosis as to the nature of the neoplasm?

MR. BROADWATER: That would be extremely difficult, but I would be inclined to favor the broad category of lymphomas. Based on statistics, lymphosarcoma of high malignancy would be most likely. I cannot be more specific than that.

MRS. HARKNESS: Cases of primary lymphosarcoma of the heart have been reported and are rare. Most of them involve the mediastinal lymph nodes and reach the heart by retrograde extension. One would ordinarily expect lymphadenopathy but I was able to find an interesting case report of a seventeen year old girl who showed no lymph node enlargement and who did have a massive pericardial effusion. She proved to have extensive involvement of the mediastinal and retroperitoneal nodes, and died with a thrombosis of the superior vena cava.

DR. SHERRY: Let us consider whether or not this patient's course is compatible with the diagnosis of a lymphoma involving the heart and pericardium. As you will recall, two weeks before the patient was admitted to Barnes Hospital she had vague complaints suggestive of an upper respiratory infection and one week later noted severe fatigue and swelling of the eyes and ankles. Although the ankle swelling responded to salt restriction, the periorbital edema persisted. Mr. Calvert, what do you think was the cause of this series of symptoms?

MR. CALVERT: Facial edema can result from a large pericardial effusion which compresses the vena cava, particularly if tamponade is present. However, the edema was fairly striking in our case, and since edema of the right arm developed subsequently, I would suspect that in addition to the pressure on the inflow tract, the disease process also was present in the mediastinum and produced an early superior vena caval syndrome.

The symptoms suggestive of an upper respiratory infection with cough malaise and fever have been described as early manifestations of neoplastic involvement of the pericardium particularly when large effusions are present with superior caval obstruction.

DR. SHERRY: As you recall, following the first admission the patient was allowed to go home relatively unimproved, only to return three days later with nausea, vomiting, and pain and swelling of the arm and neck. There was an increase in the facial and periorbital edema. Physical examination revealed swelling of the face, periorbital areas and the right side of the neck with associated neck vein distention and cyanosis. The pulse was paradoxical and the heart was markedly enlarged. Mr. Porterfield, how do you interpret these manifestations?

MR. PORTERFIELD: They suggest obstruction of the right innominate vein and an increase in the pericardial effusion. The paradoxical pulse appeared to be the result of the massive pericardial effusion, but the edema of the right arm and right side of the neck and the swelling of the right side of the face might well have been due to involvement of the right innominate vein.

DR. SHERRY: Mr. Catanzaro, do you distinguish between a pericardial effusion and cardiac tamponade.

MR. CATANZARO: Yes. Cardiac tamponade denotes acute accumulation of fluid which embarrasses the circulation. It has been observed that an acute accumulation of from 150 to 250 ml. of fluid in the pericardial sac will cause cardiac tamponade. However, one can have a rather large slowly accumulating pericardial effusion without having cardiac tamponade.

DR. SHERRY: Do you think this patient had cardiac tamponade, when she entered for the second time?

MR. CATANZARO: Yes, I think she did, as suggested by the appearance of a paradoxical pulse and a rapid deterioration in her clinical condition.

DR. SHERRY: When the patient was operated upon, she was found to have a very tense and distended pericardial sac. Following the removal of 1 L. of sanguinous fluid, she improved considerably. One hour later, a shock-like picture developed with tachycardia, tachypnea, cyanosis, electrocardiographic changes suggestive of acute cor pulmonale and the patient ultimately died. Mr. Gass, what do you think happened?

MR. GASS: The most common cause of this group of signs and symptoms is massive pulmonary embolism. However, there are other processes which might result in a similar picture, for example, massive atelectasis or pneumonia. However, I believe we are probably dealing with pulmonary embolization.

DR. SHERRY: What type of embolization?

MR. GASS: It could either be tumor material or a thrombus, but probably it was due to a thrombus which formed at the site of compression of the superior vena cava.

DR. SHERRY: Let us also consider the possibility of pericardial shock which may occur following the removal of a large quantity of pericardial fluid.

MR. GASS: If the picture were not so typical of a massive pulmonary embolus with electrocardiographic confirmation of acute cor pulmonale, we would certainly wish to consider pericardial shock. Pericardial shock usually follows a rather sudden relief of pressure and is believed to be associated with acute cardiac dilatation. Pericardial shock usually occurs in cases of constrictive pericarditis in which the myocardium has become atrophic and acute dilatation is more likely.

DR. SHERRY: Are there any other comments?

MR. PORTERFIELD: With a picture suggesting right innominate vein obstruction rather than superior vena caval obstruction, one must locate the tumor in the superior portion of the mediastium. This could of course be produced by enlarged lymph nodes, but the most common malignant tumor of the superior mediastinum is a thymoma, and many of these are lymphosarcomas. Therefore, I would like to suggest that our patient may have had a primary malignant thymoma as the cause of her illness.

MR. GASS: Several of us have given serious consideration to a Kaposi's sarcoma of the right atrium, and would not be too surprised if that lesion were found.

DR. SHERRY: We must conclude at this point. All of you agree that the patient had a malignant neoplasm, probably in the mediastinum with extension to involve the great vessels, heart, and pericardium. Most of you (eight) believe that the malignancy will prove to be a lymphosarcoma, and the rest (two) favor a malignant thymoma. Kaposi's sarcoma is also suggested as a less likely possibility but none favors it as his first choice. Tuberculous pericarditis seems unlikely although it cannot be completely excluded. Finally, you all agree that the terminal event was pulmonary embolization from a thrombus in one of the involved veins.

PATHOLOGICAL DISCUSSION

DR. JOHN MEYER: At autopsy, the right upper extremity and the face of this young white female were edematous and her nail beds were unusually cyanotic, particularly those of the right hand. Livor mortis was advanced over the face. Approximately 600 cc. of slightly cloudy, yellow fluid was found in each pleural cavity and in the peritoneal cavity. It clotted readily on standing in tubes. Firm reddish tan nodules studded the parietal pleurae over the upper lobes. (Fig. 1.) The pericardial cavity contained about 100 cc. sanguinous fluid and its serous surfaces were covered by fibrin and blood. The superior mediastinum was occupied by a large, firm, reddish tan mass of tissue. The right internal jugular and the right subclavian veins

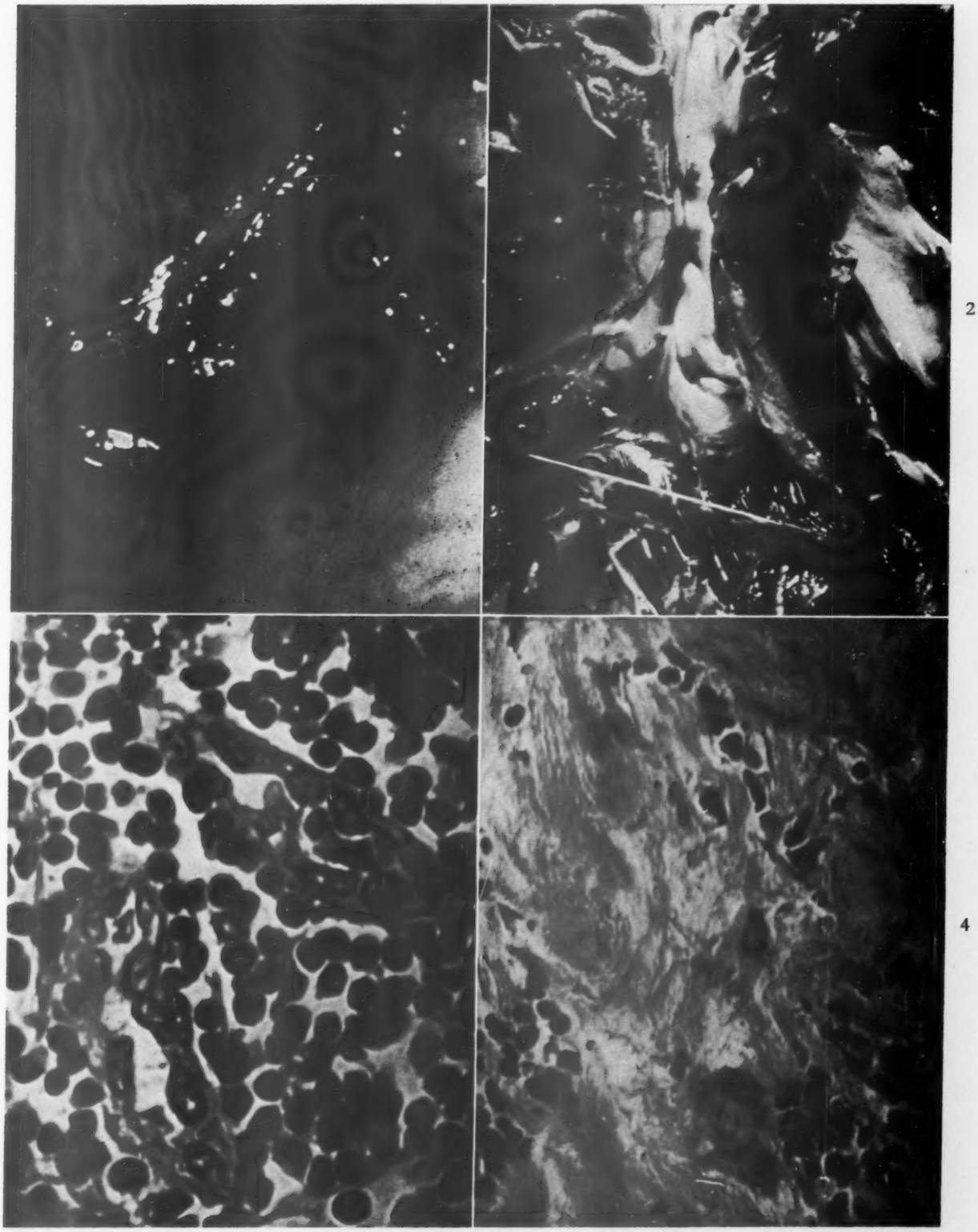

Fig. 1. Reddish tan nodules scattered over parietal pleurae of the upper pulmonic lobes.

Fig. 2. The right pulmonary artery surrounded by tumor and its greatly reduced lumen (slit of 1 mm.).

Fig. 3. The epithelial cells and collections of small round cells and lymphocytes in the tumor. Note how they surround the vessels intimately.

Fig. 4. A portion of the tumor in which a mesenchymal type of stroma was the abundant striking feature.

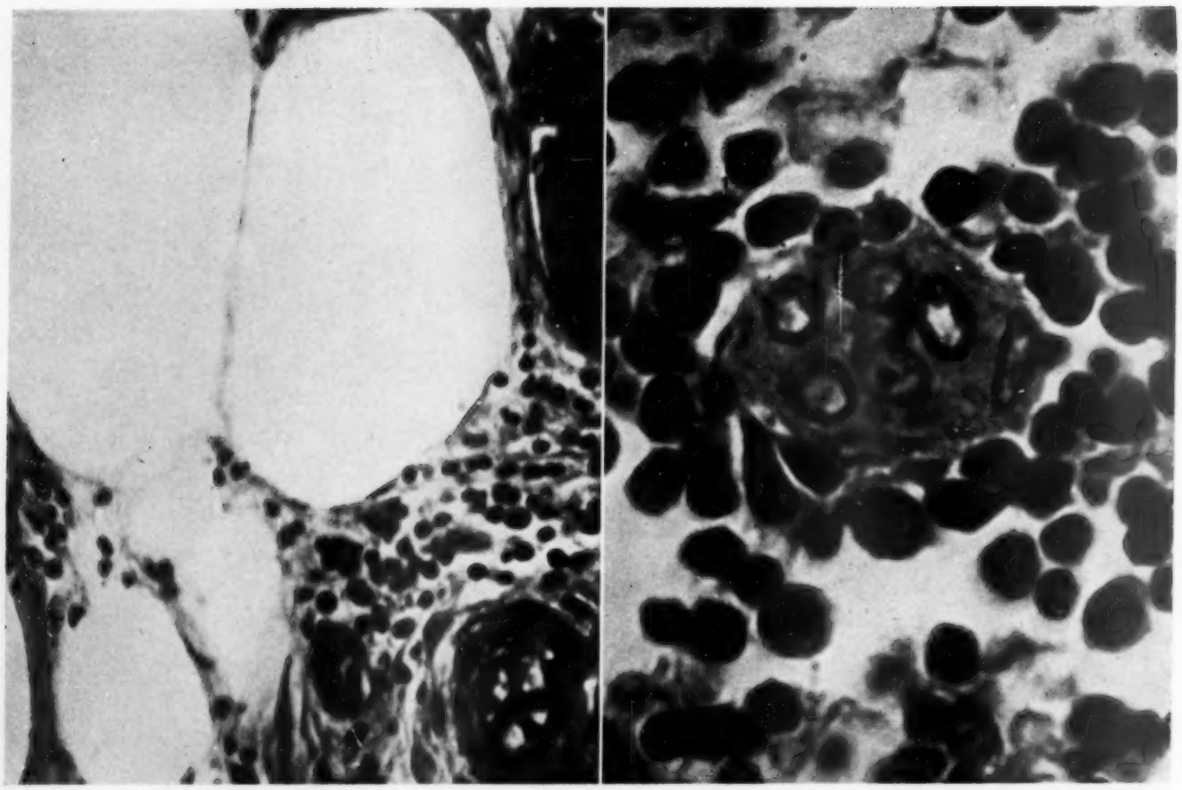

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FIG. 5. Prominent cyst formation within the tumor.

FIG. 6. A rare multinucleated cell surrounded by round cells.

were severely stenosed, and distal to the stenosis. They were distended. A thrombus was present in the right subclavian vein above its stenotic point. The corresponding veins on the left side along with the innominate veins and superior vena cava were slightly to moderately compressed by the tumor. The endocardium was covered by nodules of firm tissue which invaded the superficial subepicardial myocardium. The right ventricle was dilated and tense when the pericardium was opened, but its wall was only 3 mm. thick, whereas that of the left ventricle was 12 mm. thick. The right main pulmonary artery was surrounded by tumor and its lumen reduced to a slit only a little more than 1 mm. wide. (Fig. 2.) At the latter site was an adherent thromboembolus where a primary branch went to the lower right lobe. Several small, dark red pyramidal areas with their bases directed against the pleurae were present in the upper right lobe, although thromboemboli were not found within the arteries supplying that lobe. The lymph nodes of the posterior mediastinum were enlarged and firm but discrete. The liver (1,280 gm.) was severely congested and yellower than usual suggesting some fatty change. The spleen (190 gm.) was congested. Dr. Hartroft will present the microscopic findings.

DR. W. STANLEY HARTROFT: I will not discuss the microscopy of any of the tissues but that of the tumor because it is the most interesting and significant abnormal finding. It is a thymoma. Under the lowest power, the primary growth in the thymus exhibited considerable architectural organization. Most of the cells were small and interspersed with foci of lymphocytes. They were probably the source of the small lymphocytes found both in the biopsy specimens and in the sample of fluid.

The cytologic features of this thymoma were of considerable interest. Epithelial cells and collections of small round cells, lymphocytic in origin, could both be found. The epithelial cells were rather undifferentiated and possessed but scant cytoplasm. (Fig. 3.) They even suggested spindle forms here and there. In other parts of the tumor the mesenchymal stroma was so abundant as to form the most prominent fea-

ture. (Fig. 4.) In still other regions dedifferentiated, nearly embryonic, epithelial cells were found almost exclusively. The pattern of this tumor varies from place to place. Rather prominent features in some regions were large cystic spaces. (Fig. 5.) Greatly distended, they were very large and may have had some significance in the interpretation of the function, or lack of it, of this tumor. In some places, the vessels were rather prominent with swollen endothelial cells, but perivascular cuffing was absent, a point of some significance. A few multinucleated cells were encountered, but they were rather hard to find. (Fig. 6.) Reticulum was abundant throughout the tumor as demonstrated by silver stains. Where tumor invaded the pericardium, it more closely resembled the biopsy specimens but even in retrospect it was impossible to make a diagnosis from the latter.

Thymomas are frequently associated with myasthenia gravis particularly in older males. When this association exists, in many cases (75 per cent) the tumors exhibit certain characteristics. They are well lobulated and consist predominately of well differentiated epithelial cells containing PAS-positive material, many lymphocytes and the vessels stand out prominently by virtue of perivascular cuffs of these cells. On the other hand, thymomas unassociated with myasthenia, usually do not exhibit many of the above features. Instead they are composed chiefly of spindle cells, frequently surrounding large cystic spaces.

In our case, absence of more than occasional PAS-positive granules in the epithelial cells, absence of perivascular cuffing and presence of cystic spaces fit in with those cases of thymoma in which myasthenia is unassociated as with our young girl. Again our case today not only was the wrong sex, but too young, compared to subjects (older males) in whom the two conditions more frequently coexist. Finally, direct extension of tumor to nearby organs is usually not associated with the presence of symptoms of myasthenia. Direct extension was very prominent, both pathologically and clinically in our case.

In conclusion, this is a case of thymoma in a fifteen year old girl, involving the anterior mediastinum with extension to the cervical regions bilaterally. It produced a dramatic pericardial effusion and involved the parietal pleurae. There was severe compression of the internal jugular and right subclavian veins which explains the periorbital edema. There were thrombi in these vessels and thromboembolism of some of the pulmonary arteries. These findings together explain most of the clinical signs and symptoms although, I am not sure we have a direct explanation for the nausea and vomiting.

Final Anatomical Diagnosis. Primary: Thymoma, anterior mediastinum involving thymus, lymph nodes or mediastinum and lower anterior cervical regions bilaterally, epicardium, and pericardium; implantation of tumor on parietal pleurae; severe compression of right internal jugular and right subclavian veins and moderate compression of left internal jugular vein, innominate veins and superior vena cava; severe compression of right pulmonary artery and moderate compression of left pulmonary artery by tumor; edema of right upper extremity and right side of face, moderate; recent antemortem thrombosis of right axillary vein; adherent thromboembolus in primary division of lower left lobe pulmonary artery; multiple pulmonary infarcts, upper right lobe; bronchopneumonia, lower left lobe; congestion of liver, severe, and of lower lobe of left lung, and kidneys, moderate; fatty metamorphosis of liver, severe. *Accessory:* Double right coronary arteries; intimal lipoidosis of abdominal aorta, slight; asymmetry of skull, moderate.

Case Reports

A Case of Massive Edema in Association with an Aldosterone-Secreting Adrenocortical Adenoma*

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A SYNDROME attributed to excessive secretion of aldosterone associated with the presence of an adenoma, carcinoma or hyperplasia of the adrenal cortex has been described by Conn [*1*]. In this syndrome the clinical consequences of the renal wastage of potassium are much more dramatic than are those of retention of sodium, despite the fact that during short-term administration to man and experimental animals aldosterone is much more active in causing sodium retention than potassium excretion [*2*].

In striking contrast with the accepted features of Conn's syndrome is the case, to be described, of a patient with a ten-year history of massive edema associated with extreme sodium retention and very high urinary excretion of aldosterone, with normal serum electrolytes and normal blood pressure, in whom an aldosterone-secreting adrenocortical adenoma was found at operation. Certain aspects of this case have been previously reported [*3–6*].

CASE REPORT

M. L. (PBBH No. 5A246), a registered nurse was twenty-seven years old when she first entered the Medical Service of the Peter Bent Brigham Hospital in December, 1945, under the care of Dr. P. J. O'Hare. She had experienced a normal childhood, suffering from measles, mumps, chickenpox and whooping cough without sequelae. She had always been overweight as a child; all the members of her family tended to be obese. In her late teens she had bilateral varicose veins treated by injection. She had an appendectomy at the age of twenty-one. At the age of twenty-three generalized dermatitis developed following the treatment of eczema with a sulphonamide ointment. During the four years preceding this admission she had had several attacks of sore throat and two attacks of severe tonsillitis; these were treated with argyrol, no sulphonamides or penicillin being administered. Between the ninth and fifth months before admission she had reduced her weight from 100 to 85 kg. by dietary restriction.

Five months before admission she noted that her right leg became swollen towards the end of the day; two weeks later her left leg began to swell. During the next three to four weeks the edema spread to her thighs and sacrum and within three months it had spread to her face. She had no exertional dyspnea at this time nor any renal symptoms, but two months before admission she became breathless on exertion, experienced a feeling of tightness in the chest and was almost bedridden.

One month before admission she was admitted to a hospital in New Hampshire for investigation. The report from this hospital stated that her urine was acid, of specific gravity 1.020, and contained a few pus cells and squamous epithelial cells. No mention was made of albuminuria. Her heart was moderately enlarged by x-ray and an electrocardiogram was reported as "showing evidence of a weakened myocardium." No data were given for blood pressure or blood chemistries. An attempt was made to digitalize her but this was abandoned because of nausea.

On admission to the Peter Bent Brigham Hospital the patient had generalized edema, weighing 92 kg. (Fig. 1), and was orthopneic. She had bilateral pleural effusions and ascites. Her heart was not enlarged by x-ray examination. Her blood pressure was 122/82 mm. Hg. The venous pressure was normal. Electro-

* From the Peter Bent Brigham Hospital, Boston, Massachusetts, and the Department of Medicine, Harvard Medical School. Supported in part by Grants from the John A. Hartford Foundation, Inc., New York City; the National Institutes of Health, United States Public Health Service, Bethesda, Maryland, and the Eugene Higgins Trust Fund of the Harvard Medical School.

cardiogram showed low voltage curves. The liver edge was palpable beneath the right costal margin. The laboratory data are shown in Table I.

During the first thirty hospital days her urine was consistently free of protein; she did, however, develop proteinuria when she had transient bouts of cystitis and also following the infusion of human albumin.

Her main disability at this time was dyspnea due to her pleural effusions. Over the course of the next two years 31 L. of pleural fluid with an average protein content of 2.5 per cent was removed during her repeated hospital admissions; in addition, she had numerous (at one period, weekly) thoracenteses at home. The pleural cavities were obliterated by fusion of the pleural membranes in 1947 (Dr. Blodgett) and the patient was not further troubled by pleural effusions.

TABLE I
LABORATORY DATA, 1945 ADMISSION

Blood:	
Hematocrit	44 per cent
Hemoglobin	14.8 gm. per cent
Erythrocyte sedimentation rate	22 mm. in one hour
Mean corpuscular volume	81 cubic microns
Mean corpuscular hemoglobin content	35 $\mu\mu g$
White blood cells	6400/mm.^{3} with normal differential
Blood Chemistries:	
Urea nitrogen	10 mg./100 ml.
Non-protein nitrogen	26 mg./100 ml.
Serum chloride	102 mEq./L.
CO_2	26.3 mMol/L.
Ca	5.4 mEq./L.
P	1.9 mMol/L.
Serum proteins	total: 5.0 gm./100 ml. (copper sulphate method) albumin: 3.1 gm./100 ml.
Cholesterol	441 mg./100 ml.
Urine:	
Specific gravity	1.010–1.027
Protein	0–0.23 gm./L.
Sediment	occasional white blood cells, no red blood cells or casts
Chloride	36 mEq./day
PSP excretion	40 per cent in two hours
Intravenous pyelography	normal
Basal metabolic rate	−6 per cent
Vital capacity	1300 ml.
Venous pressure	130 mm. H_2O
Circulation time	17 second (decholin®)
Inulin and PAH clearances reported as "normal"	
Throat culture	Staphylococcus aureus
Electrocardiogram	low voltage curves
Pleural fluid	total protein 2.7 gm./100 ml. white blood cells 580/mm.^{3} (98 per cent lymphocytes)
Edema fluid	total protein 1.3 gm./100 ml.

FIG. 1. Appearance of patient's legs and thighs in 1947.

The following substances were used in attempts to produce a diuresis during the years 1945 to 1948: digitalis, urea (60 gm./day), ammonium chloride, mercurials, thyroid, typhoid vaccine, parathyroid extract, chorionic gonadotrophin, ACTH, cortisone, salt-poor human globin, salt-poor human albumin (25 gm. intravenously), mannitol, 12 per cent dextran, methionine, wheat germ oil, pyribenzamine, mictine, pitressin,® dialysis on the artifical kidney. Apart from an initial moderate diuresis with urea and during the first course of salt-poor human albumin, none was successful. Southey's tubes were the most effective method of reducing her edema. Mercurials could not be used because of hypersensitivity.

On her third hospital admission (September 22, 1947 to May 23, 1948) extensive investigations were undertaken to determine the cause of her edema. Renal function studies (Dr. S. Gibson) showed a glomerular filtration rate (C_{inulin}) of 115 ml./minute and renal plasma flow (C_{PAH}) of 455 ml./minute. The antidiuretic hormone activity of the urine was

reported as "not excessive" (Dr. H. G. Kunkel, Rockefeller Hospital, New York). She had no albuminuria to qualitative testing and a quantitative test showed only 23 mg. per L. Determination of serum proteins on this admission gave a total of 5.1 gm./100 ml. with a serum albumin of 3.1 gm. Her pleural fluid at this time contained a total protein of 3.9 gm./100 ml. with an albumin content of 2.1 gm. Her edema fluid contained a total protein of 2.0 gm./100 ml., with an albumin of 1.4 gm. The distribution of protein fractions was studied in greater detail by means of the Tiselius electrophoresis apparatus (Dr. E. Cohn, Harvard Medical School); the comparison of serum and tissue fluid is shown in Table II. After the infusion of 50 gm. of human albumin intravenously daily for ten days the protein content of the edema fluid rose from 2.1 gm./100 ml. to 3.4 gm./100 ml., the serum protein rose from 5.1 to 6.5 gm./100 ml. Ten days later the edema-fluid protein had returned to 1.9 gm./100 ml. It was on the strength of this observation and of the pattern of distribution of proteins between plasma and tissue fluid that this patient's edema was believed to be on the basis of abnormal capillary permeability to proteins [*3*]. Subjectively, the administration of human albumin was accompanied by increased dyspnea with reduction of vital capacity and by headache. A skin biopsy was taken on this admission and was reported as follows (Dr. J. Boggs): "Blood vessels show only slight changes. Occasional vascular channels show swelling of endothelium but this is not a marked change. Around an occasional vessel there is a slight amount of chronic inflammatory cell infiltration."

TABLE II
TISELIUS FRACTIONATION OF SERUM AND TISSUE FLUID PROTEINS

Fractions	Normal Serum*	Patient Serum*	Tissue Fluid*	Ratio of Tissue Fluid to Serum Protein ×100
Albumin	3.4 –4.3	2.08	1.35	65
α_1 Globulin	0.38–0.87	0.30	0.08	27
α_2 Globulin	0.57–0.94	0.78	0.12	15
β Globulin	0.73–1.38	0.99	0.16	16
γ Globulin	0.59–1.46	0.36	0.21	58
Fibrinogen	0.3	0.68	0	0

* Expressed as grams per 100 ml. fluid.

In 1949 treatment with cation exchange resins was instituted. On receiving 60 to 100 gm./day of permutit resin for seven weeks the patient lost 10 kg. in weight but therapy had to be discontinued because of symptoms of potassium and calcium depletion (serum K = 2.0, Ca = 3.3 mEq./L.).

From 1949 to 1956 intermittent therapy with cation exchange resins in the potassium ammonium cycle, in combination with a low salt diet (2.0 gm. NaCl), and supplementary potassium chloride and calcium phosphate proved to be the most effective form of treatment for this patient, minimizing the gain in weight and lengthening the interval between hospital admissions. During each twenty-day period of resin administration she achieved a 3 to 4 kg. weight loss. Southey's tubes still proved the most effective method of removing edema fluid from the extremities when in hospital, each application resulting in a 2 to 4 kg. weight loss in twenty-four to forty-eight hours.

TABLE III
ACTH TEST PERFORMED IN 1947

Twenty-four Hour Periods	17-Ketosteroids (mg./24 hours)	Urinary Na (mEq./24 hours)
Control day 1	1.5	4
Control day 2	...	2
ACTH 10 mg. i.m.* 6 hourly	...	27
ACTH 10 mg. i.m. 6 hourly	8.9	13

* Intramuscularly.

By 1952 her condition had improved considerably and she returned to duty as a private nurse, working eight hours a day; she has continued working since then, with yearly hospital admissions directed at removal of edema fluid. The fluctuations in her weight over the years are shown in Figure 2.

CLINICAL STUDIES

With the availability of a method for the measurement of aldosterone in urine [*13*] readmission of the patient was arranged in January, 1956, to study the role, if any, played by aldosterone in the pathogenesis of her edema. The sodium content of her urine had been recorded on two previous occasions only; in 1947, when on a "salt-poor diet," the twenty-four-hour urine sodium content was 7.8, 14.7, 8.5, 2.9, 2.2, 3.4, and 5.2 mEq. on seven consecutive days. Again in the same year the urine sodium content on two occasions was 4 and 2 mEq./day when on a constant intake of 48 mEq./day. However, in 1948 the daily administration of as much as 700 mEq. of sodium as a mixture of lactate and bicarbonate had resulted in achievement of sodium balance but only when the highest levels of intake were reached. Upon reduction of the sodium intake a lowered excretion and positive sodium balance promptly recurred. An ACTH test was performed on this occasion, with results shown in Table III. The urinary aldosterone level of a urine specimen sent from home in December, 1955, on a sodium intake of 40 to 50 mEq./day, was 52 μg./

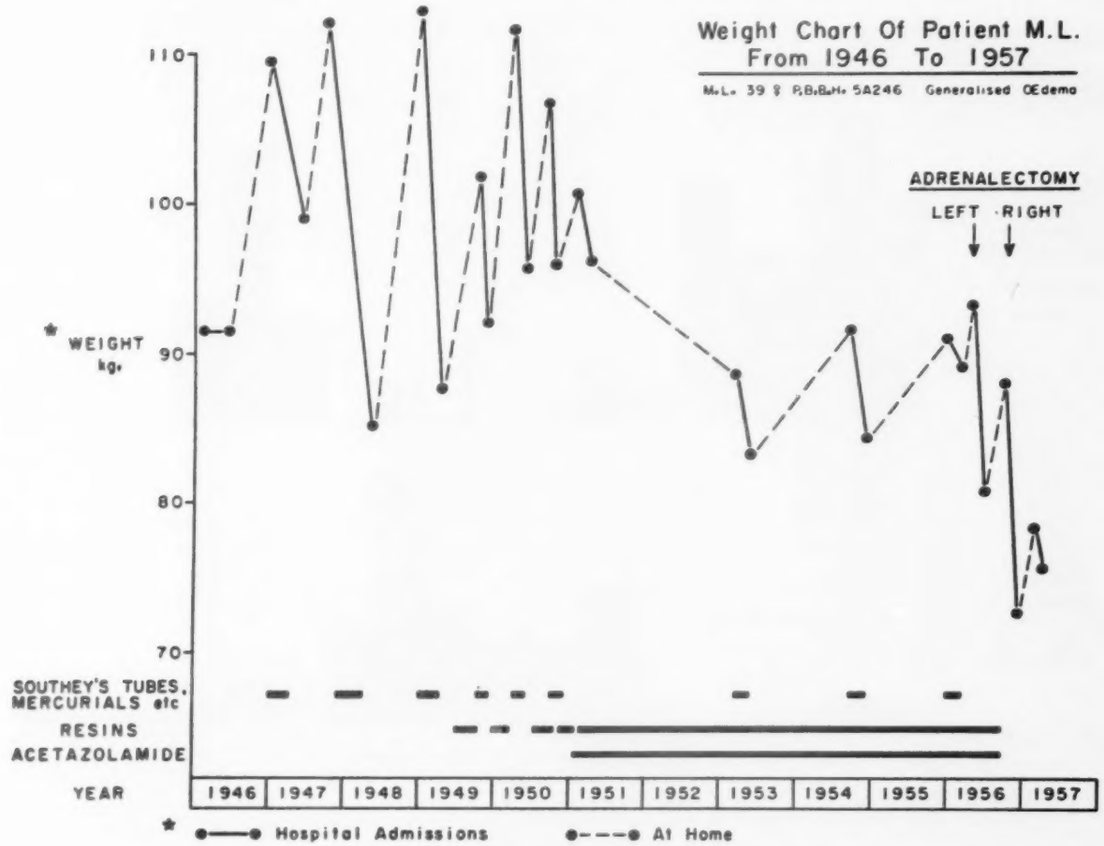

FIG. 2. Weight chart of patient during the years 1946 to 1957.

twenty-four hours (normal values 1 to 10 μg.). The aldosterone and sodium excretions on the first five days of her admission, on a sodium intake of 9 mEq./day, were as follows:

Date	Urinary Sodium* (mEq./24 hr.)	Urinary Potassium (mEq./24 hr.)	Urinary Aldosterone (μg./24 hr.)	Weight (kg.)
1/6/56	12	30	87	90.5
1/7/56	5.6	44	123	90.4
1/8/56	3.0	62	66	90.6
1/9/56	2.1	75	70	90.4
1/10/56	1.4	80	98	90.0

* Intake Na: 9 mEq./day.

When the dietary intake of sodium was restored to 105 mEq./day the excretion of high levels of aldosterone continued, together with low urinary sodium levels despite the increased intake. There was a weight gain of 4.3 kg. over five days.

Date	Urinary Sodium* (mEq./24 hr.)	Urinary Potassium (mEq./24 hr.)	Urinary Aldosterone (μg./24 hr.)	Weight (kg.)
1/29/56	1.7	38	20	86.6
1/30/56	3.0	62	116	87.4
1/31/56	2.5	78	73	88.5
2/1/56	3.2	75	25	89.1
2/2/56	4.1	56	66	90.9

* Sodium intake 135 mEq.

In spite of this high level of excretion of aldosterone, sudden restriction of sodium intake from 135 mEq./day to 9 mEq./day caused a further increase in the level of excretion as shown in Table IV.

The salivary Na/K ratio during this period ranged from 0.11 to 0.25 at all levels of sodium intake. This is a low ratio for subjects on a normal sodium intake.

The very low level of urinary sodium excretion, irrespective of sodium intake, is noteworthy as was the failure to produce a sodium diuresis or lowering of

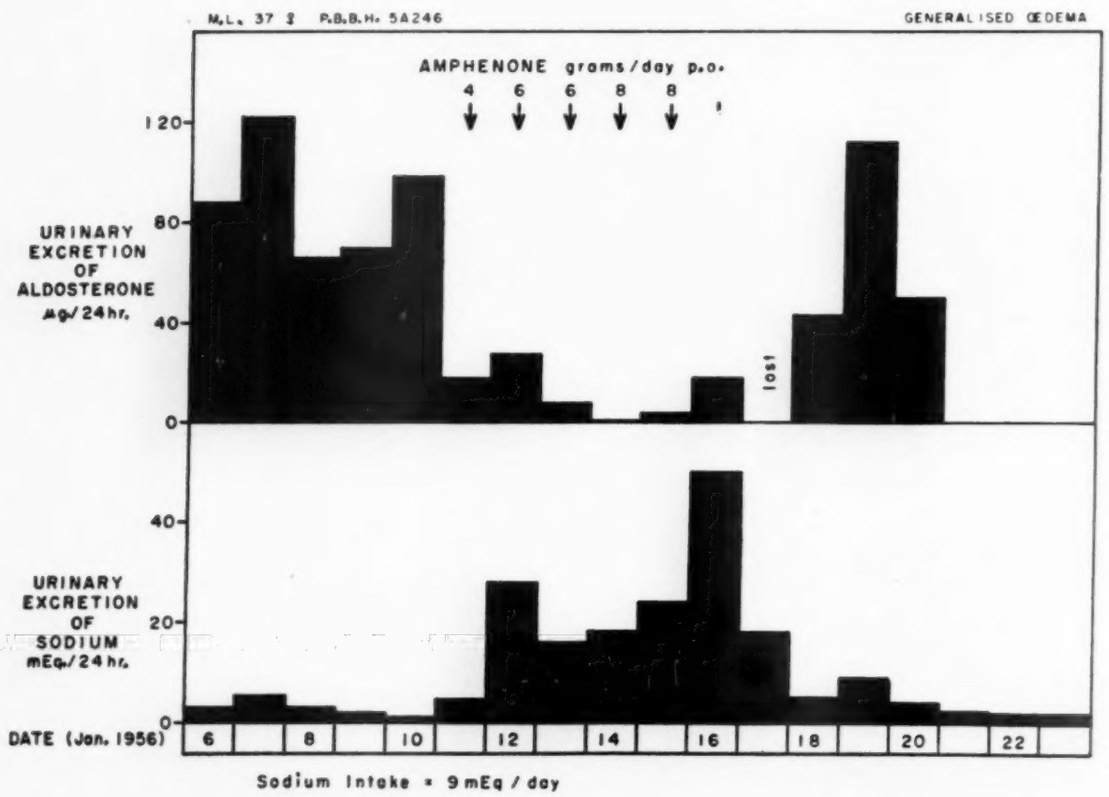

FIG. 3. Sodium diuresis resulting from amphenone administration.

aldosterone excretion by the administration of 12 per cent dextran (750 ml. intravenously over two days), ACTH (Table v) and prednisone (100 mg./day). Amphenone B (which suppresses the synthesis of adrenocorticosteroids) produced a good sodium diuresis (Fig. 3), especially when given in conjunction with prednisone. (Fig. 4.) These observations led to the conclusion that the high level of aldosterone excretion (and so presumably of secretion) was an important factor in the marked sodium retention exhibited by this patient. It was therefore decided to explore her adrenal glands.

The patient was readmitted on March 21, 1956. Pertinent clinical and laboratory data at this time are listed in Table VI. On April 3, 1956, the left adrenal was explored first (because of a slight displacement of the upper pole of the left kidney seen on tomograms). An adenoma, measuring 1.5 × 1.0 cm. and weighing 2 gm., was found and the entire adrenal removed (Dr. J. H. Harrison). Pathological report of left adrenal gland (Dr. G. W. Curtis) was as follows:

TABLE IV
RESPONSE OF ALDOSTERONE EXCRETION TO LOW SODIUM DIET

Date	Sodium Intake (mEq.)	Sodium Excretion (mEq.)	Aldosterone Excretion (µg.)
1/30/56	135	3.0	116
1/31/56	135	2.5	73
2/1/56	135	3.2	25
2/2/56	135	4.1	66
2/3/56	9	4.4	63
2/4/56	9	2.2	107
2/5/56	9	1.6	137
2/6/56	135	4.6	45

TABLE V
ACTH TEST BEFORE REMOVAL OF LEFT ADRENAL

Twenty-four Hour Periods	17-Hydroxy-corticoids*	17-Keto-steroids*	Urinary Na†	Urinary K†	Urinary Aldosterone‡
Control day 1.....	6.5	2.6	4.2	72	116
Control day 2.....	5.8	3.0	3.7	61	60
ACTH 25 units over 8 hours.....	35.2	8.2	8.1	102	50
ACTH 25 units over 8 hours.....	54.0	13.9	2.7	46	113

* mg./24 hour.
† mEq./24 hour.
‡ µg./24 hour.

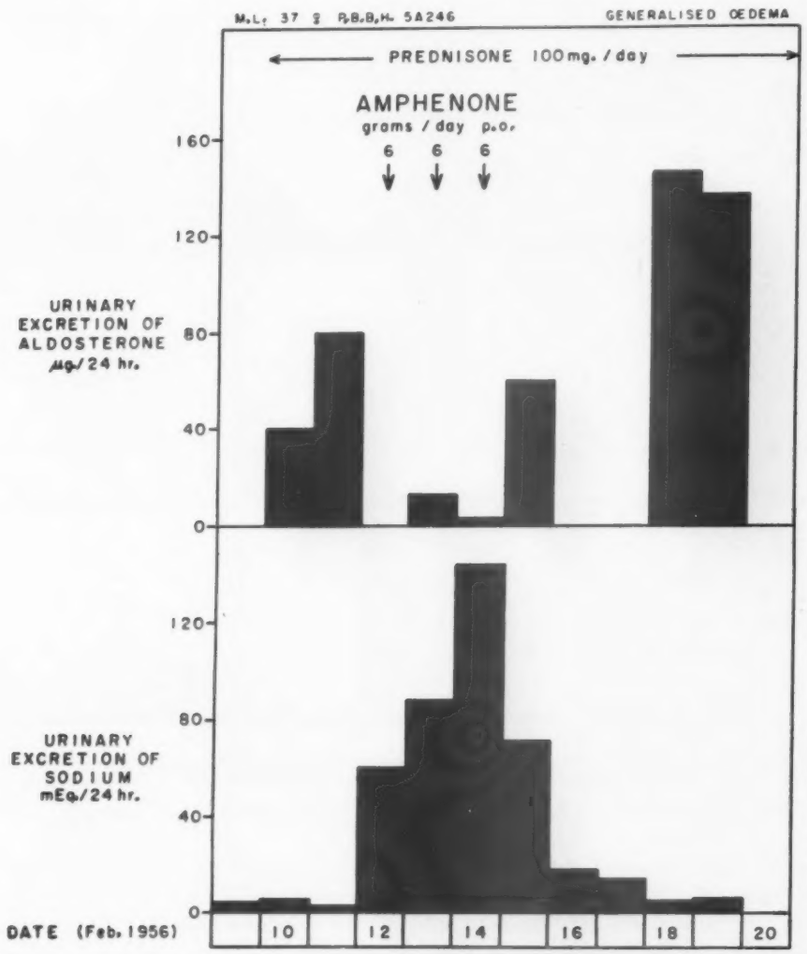

FIG. 4. Sodium diuresis obtained during simultaneous administration of amphenone and prednisone.

"The specimen consists of the left adrenal gland weighing 6.9 grams and measuring 6 × 3 × 0.3 cm. At one pole is an adenoma measuring 1.5 × 1.0 cm., weighing 2 grams. On section the adenoma is yellow with small irregular dull brown patches. Microscopic examination: The cortex reveals a prominent glomerulosa consisting of large cells with cytoplasm composed of large vacuoles. The fasciculata is composed of cells of two types, one similar to those of the glomerulosa the other consisting of cells with finely vacuolated eosinophilic cytoplasm. The reticularis is difficult to define. The adenoma is composed mostly of large cells with large cytoplasmic vacuoles arranged in small groups or short cords. Patterns of all three zones of the adrenal are seen but none predominates. The medulla is composed of large cells with a fairly basophilic cytoplasm." The aldosterone content of the tumor and of an equal weight of the adrenal gland tissue was determined. The adenoma contained 3 µg. of free aldosterone per gm. of tissue; no demonstrable aldosterone was present in the non-adenomatous portion of the left adrenal gland. Biopsy specimen of the left kidney showed arteriosclerosis with focal tubular atrophy.

Immediately following removal of the adenoma the patient experienced a profuse water and sodium diuresis. (Fig. 5.) Indeed, so great was the sodium diuresis that 9-α-fluorohydrocortisone was administered to prevent acute sodium depletion. An ACTH test one week after operation showed a satisfactory response from the remaining adrenal. (Table VII.)

For ten postoperative days the patient's sodium excretion about equalled her sodium intake (60 to 70 mEq./day) but slowly fell to 20 mEq./day. On an intake of 9 mEq./day her sodium excretion ranged from 20 to 35 mEq./day and her sodium excretion did not cut down to the level of intake, as would occur in a normal person. She was not receiving any cortisone therapy at this time.

Determinations of the amount of aldosterone excreted in the patient's urine were made at intervals during the postoperative period. On the day follow-

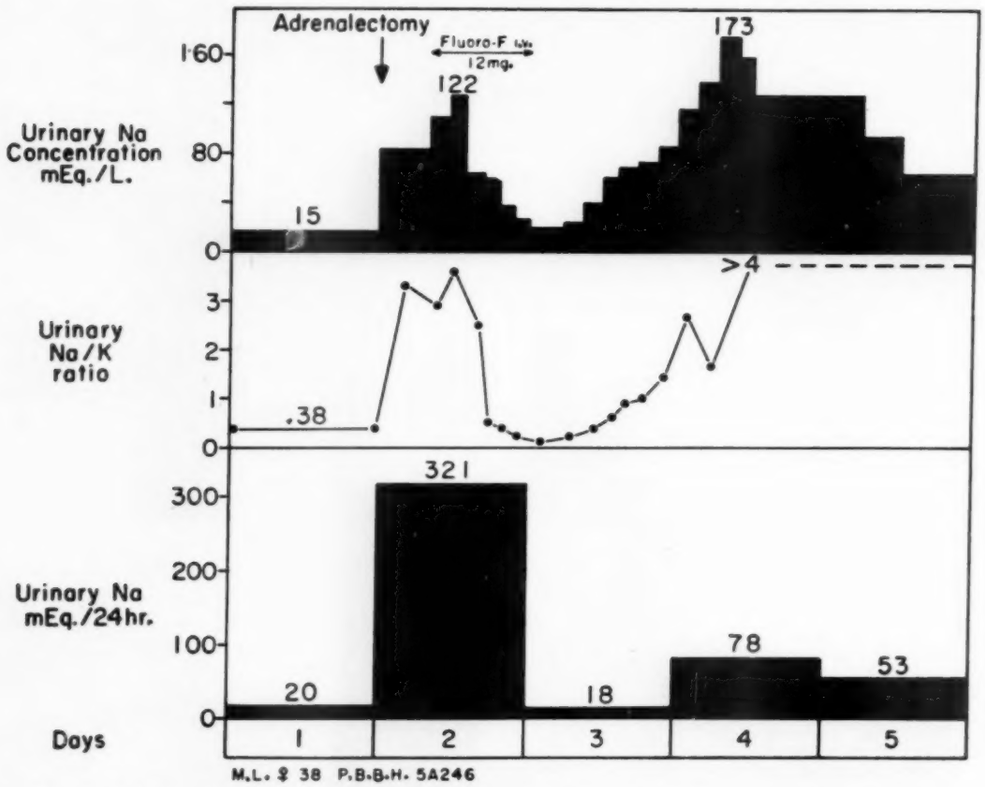

FIG. 5. Sodium diuresis which immediately followed removal of adrenocortical adenoma.

ing operation no measurable level could be demonstrated. Six weeks after operation levels up to 30 μg./twenty-four hours were found. These values were observed with a sodium intake of 140 mEq./day. At this time the patient was able to adjust her urinary sodium output to balance the sodium intake (Fig. 6); this she had been unable to do before the removal of the adenoma. She also responded to acetazolamide by a large sodium diuresis (322 mEq.) on a sodium intake of 9 mEq.

Since the patient was anxious to lose weight (i.e., edema fluid) as quickly as possible, she was given a diet containing 35 mEq. of sodium. On this regimen weight was lost at first but within a few weeks spontaneous weight loss ceased. The administration of acetazolamide, later with the addition of prednisone (10 mg./day), and finally of acetazolamide on two days and a cation exchange resin (amberlite®) on four days per week was required to produce a sustained

TABLE VI
CLINICAL AND LABORATORY DATA ON ADMISSION MARCH, 1956
(BEFORE LEFT ADRENALECTOMY)

Weight	92.7 kg.
Blood pressure	100–120/50–60—no cardiac enlargement
Blood Chemistries:	
Serum Na	137 mEq./L.
K	4.3 mEq./L.
Cl	101 mEq./L.
CO_2	25.5 mMol./L.
Cholesterol	233 mg./100 ml.
Urea N	6 mg./100 ml.
Total protein	5.4 mg./100 ml.
Albumin	3.6 mg./100 ml.
Urine:	
No albumin	
No sugar	
17-hydroxycorticoids	6.5 mg./24 hour
17-ketosteroids	2.8 mg./24 hour

TABLE VII
ACTH TEST AFTER REMOVAL OF LEFT ADRENAL

Twenty-four Hour Periods	17-Hydroxy-corticoids*	17-Keto-steroids*	Urinary Na†	Urinary K†	Urinary Aldosterone‡
Control day 1	6.1	3.4	34	25	1
Control day 2	5.0	1.9	27	24	2.5
ACTH 25 units over 8 hours	10.9	2.2	12.6	45	0
ACTH 25 units over 8 hours	33.7	7.5	3.8	26	10

* mg./24 hour.
† mEq./24 hour.
‡ μg./24 hour.

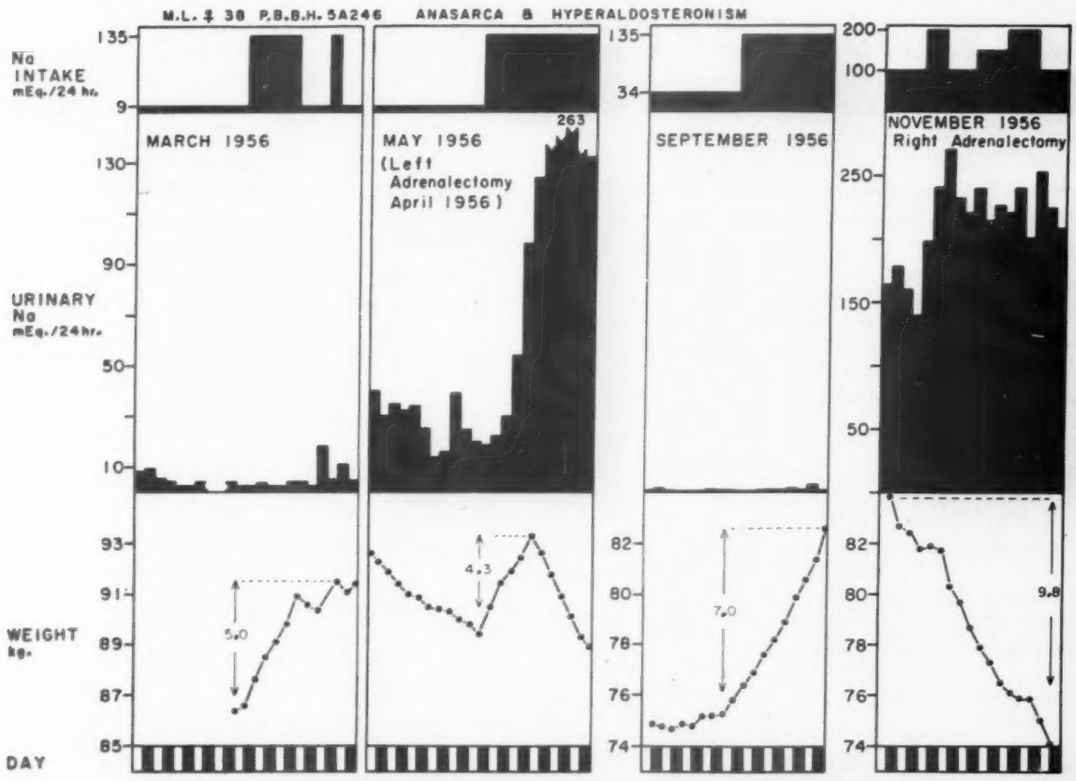

FIG. 6. Response to sodium loading before and after successive adrenalectomies.

weight loss. (Fig. 7.) Finally, three and a half months after removal of the adenoma, at a time when her weight had fallen from 90.9 kg. to 73 kg., no further weight loss could be obtained without the patient exhibiting symptoms suggestive of sodium depletion, weakness, tiredness, nausea and muscle cramps.

She was accordingly readmitted to hospital in September, 1956. Relevant clinical and laboratory findings found on this, her fourteenth, admission are shown in Table VIII. The high serum potassium may have resulted from long-continued therapy with cation exchange resins in the potassium-ammonium phase. Her urinary excretion of sodium was found to be less than 1 mEq. a day, on an intake of 35 mEq. a day, and while taking prednisone, 10 mg. a day. When her sodium intake was increased to 138 mEq./day, her sodium excretion continued to be less than one mEq./day. (Fig. 6.) While still on a sodium intake of 138 mEq./day, her prednisone was increased to 100 mg./day; on this there was a slight increase of sodium excretion which then ranged from 4.0 to 9.7 mEq./day. The addition of amphenone, in doses of 6 gm./day, resulted in a sodium diuresis of up to 113 mEq./twenty-four hours. The administration of ACTH caused no increase in sodium excretion; neither did the administration of 750 ml. of 12 per cent dextran. Her aldosterone excretion on ten consecutive days, shown in Table IX, ranged from 15 to 65 μg./twenty-four hours. With amphenone her aldosterone excretion was reduced to 0 μg./twenty-four hours. Renal function studies in October, 1956, (Dr. J. Young) showed that her inulin clearance was 110 ml./minute and PAH clearance 415 ml./minute. These are almost identical with the figures obtained in 1948 and in March, 1956. It was surprising to find that she excreted 3 per cent of her filtered load of sodium. On this, as on previous occasions, the clearance studies were associated with a sodium diuresis. The cause of this is not clear since her sodium excretion was very little increased by an osmotic diuresis resulting from the infusion of mannitol, nor was it increased by a water load. Her pattern of renal and adrenal responses to the various tests employed at this time was almost identical with that present before removal of the adrenocortical adenoma seven months previously. It differed from that present immediately after the removal of the adenoma in one important respect, namely, that her urinary excretion of sodium was then within the normal range and she could adjust her output to match her intake. On the basis of this similarity, it was decided to remove her remaining adrenal gland.

At operation (November 5, 1956) a normal sized adrenal gland was found and removed (Dr. J. H. Harrison). The pathological report (Dr. G. W. Curtis) read: "The specimen received consists of part of the

right adrenal, measuring 1 × 2 cm. The medulla is very narrow, the cortex measures 0.15 cm. in width. Microscopic examination: the gland is composed chiefly of zona fasciculata. The cells are large with vacuolated cytoplasm. The same cell type is seen in the zonae glomerulosa and reticularis, both of which are poorly defined. A nodule of cortical reduplication is seen which is composed of the same cell type. The predominant cell type is the same as that seen in the previously removed adenoma. Conclusion: hypertrophy of right adrenal gland."

Immediately after the adrenal gland had been removed there was, as on the occasion of the first operation, a sodium diuresis which lasted about twelve hours. (Fig. 8.) During this period 222 mEq. of sodium were excreted despite the administration of 100 mg. of cortisone intramuscularly and 200 mg. of hydrocortisone intravenously. During the succeeding twelve hours only 2 mEq. of sodium were excreted. The quantities of sodium excreted in the immediate postoperative period were as follows:

TABLE VIII
CLINICAL AND LABORATORY DATA, ON ADMISSION OF SEPTEMBER, 1956

Weight	75.5 kg.
Blood pressure	100/64—no cardiac enlargement
Vital capacity	2.4 L.
Blood Chemistries:	
Serum Na	131 mEq./L.
K	5.2 mEq./L.
Cl	100 mEq./L.
CO_2	22.4 mMol./L.
Urea N	10 mg./100 ml.
Cholesterol	245 mg./100 ml.
Total protein	5.5 gm./100 ml.
Albumin	4.3 gm./100 ml.
Urine:	
No albumin	
No sugar	
Numerous epithelial cells	
Electrophoretic Pattern of Serum Proteins (Dr. D. M. Surgenor):	
Albumin	51 per cent (normal = 63.3 per cent)
α_1 globulin	7.4 per cent (normal = 4.8 per cent)
α_2 globulin	13.7 per cent (normal = 7.5 per cent)
β globulin	17.8 per cent (normal = 5.3 per cent)
γ globulin	10.0 per cent (normal = 11.6 per cent)

TABLE IX
URINARY EXCRETION OF SODIUM AND ALDOSTERONE BEFORE SECOND OPERATION

Date	Sodium Intake (mEq./day)	Sodium Excretion (mEq./day)	Aldosterone (μg./24 hr.)
9/15/56	35	0.4	65
9/16/56	35	0.4	44
9/17/56	35	0.4	51
9/18/56	35	0.9	60
9/19/56	35	0.7	48
9/20/56	35	0.6	45
9/21/56	136	0.4	15
9/22/56	136	0.5	25
9/23/56	136	0.4	24
9/24/56	136	0.8	52

Date	Replacement Therapy	Sodium Intake	Urinary Na (mEq./24 hr.)	Urinary K (mEq./24 hr.)
11/5/56	(Operation)			
	Cortisone 100	...		
	Hydrocortisone 200		224	161
11/6/56	Cortisone 200	...	5.4	24
11/7/56	Cortisone 150	14	57	22
11/8/56	Cortisone 100	20	41	28
11/9/56	.....	29	19	20
11/10/56	Cortisone 87½	27	34	38
11/11/56	.....	29	18	19
11/12/56	Cortisone 75	29	41	27
11/13/56	Cortisone 75	30	127	53
11/14/56	Cortisone 62½	29	121	77
11/15/56	Cortisone 62½	63	164	63
11/16/56	Cortisone 62½	64	178	82
11/17/56	Cortisone 62½	104	163	73
11/18/56	Cortisone 62½	96	140	64
11/19/56	Cortisone 62½	206	196	75
11/20/56	Cortisone 50	206	240	81
11/21/56	Cortisone 50	104	271	94

From this time on, the level of sodium excretion has ranged from 210 to 240 mEq./day, irrespective of sodium intake (Fig. 9) which ranged from 102 to 205 mEq./day. The administration of 0.1 mg. of fluorohydrocortisone was effective in reducing her sodium excretion. Between the day of operation (November 5, 1956), and her discharge on December 12, 1957, she lost 16 kg. in weight. She was sent home on a sodium intake of 205 mEq. (12 gm. NaCl), taking 50 mg. of cortisone daily and 0.1 mg. of fluorohydrocortisone on alternate days. No aldosterone could be detected in a 10-L. pool of urine collected after operation.

At home she lost weight steadily but when she reached a weight of 73 kg. she began to experience nausea, weakness and muscle cramps. The administration of 500 mg. of acetazolamide, resulting in a 1.5 kg. weight loss, made her feel very weak. The finding of a serum sodium of 126 mEq./L. (and serum K of 6.1) confirmed the clinical impression of hyponatremia despite the continuing presence of edema.

Relevant laboratory findings on readmission (January 25, 1957 to February 25, 1957) are given in Table x. The patient felt well when taking 205 mEq. of sodium and 50 mg. of cortisone a day. On this regimen

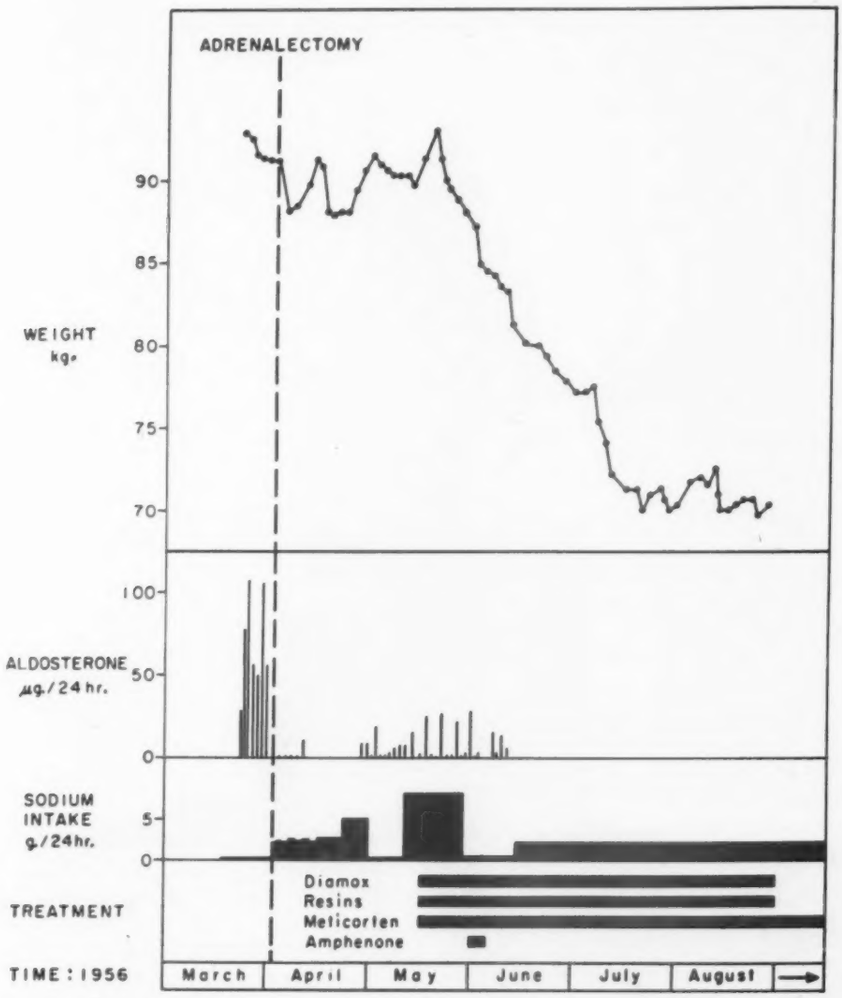

FIG. 7. Weight loss following removal of adrenocortical adenoma.

her weight remained stationary; her legs and thighs were still edematous. Attempts were made to enable her to lose weight without developing symptoms. Prednisone was substituted for cortisone and deoxycorticosterone for fluorohydrocortisone at different levels of sodium intake but on all occasions further loss of weight was associated with symptoms of nausea, weakness and muscle cramps.

A total body composition study (Dr. K. Olesen) at this time gave results shown in Table XI. The low value for total body water (43.4 per cent of body weight) probably indicates an excess of body fat. Her exchangeable sodium was normal when expressed as per liter total body water but the residual sodium was low and the extracellular sodium concentration was low. Residual sodium (total sodium minus extracellular sodium) was extremely low, indicating that the sodium store in bone was empty or that it was not exchangeable with isotopic sodium. The exchangeable potassium was also low, expressed in terms either of body weight or body water. The intracellular potassium was low; the extracellular potassium concentration was high normal, due to a raised serum potassium.

TABLE X
CLINICAL AND LABORATORY DATA, ON ADMISSION OF JANUARY, 1957

Weight	77.7 kg.
Blood pressure	108/70—no cardiac enlargement
Blood Chemistries	
Serum Na	126 mEq./L.
K	6.1 mEq./L.
Cl	100 mEq./L.
CO_2	27 mMol./L.
Blood urea N	20 mg./100 ml.
Cholesterol	262 mg./100 ml.
Urine:	
No albumin	
No sugar	

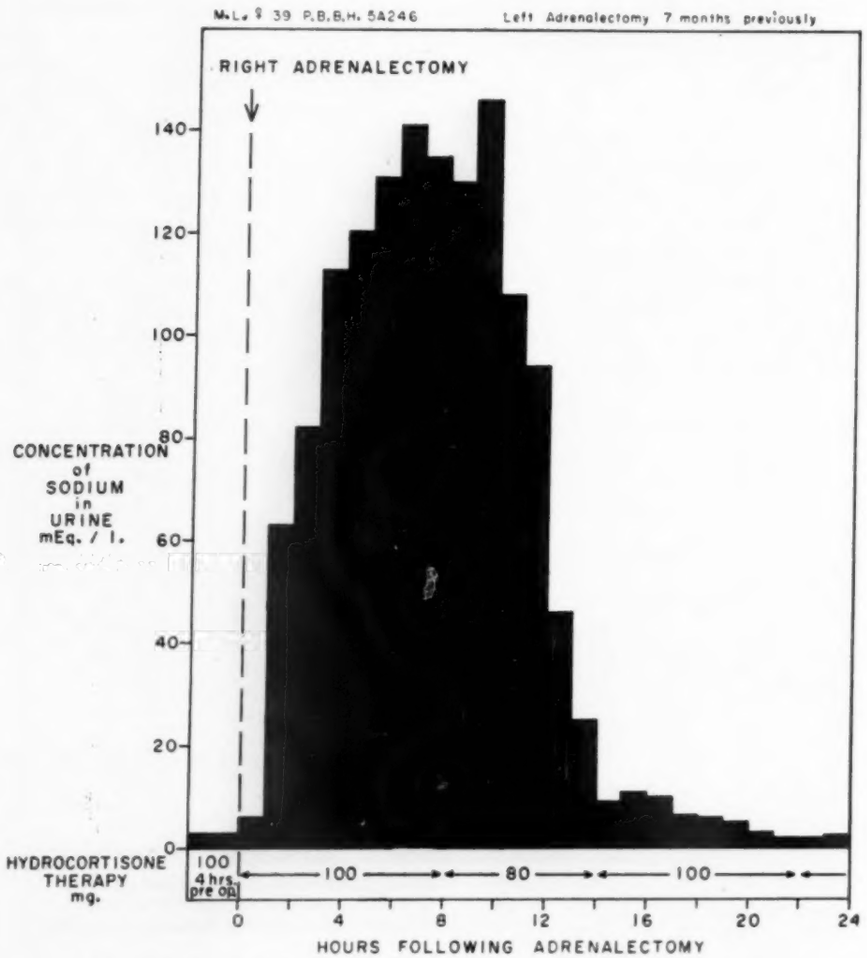

FIG. 8. Sodium diuresis immediately following second adrenalectomy.

No further attempts at weight reduction were made in the hope that internal readjustments would occur over the course of time and it would then be possible to reduce her sodium intake and produce a sodium diuresis without provoking symptoms of sodium depletion. The change from a daily dose of 50 mg. of cortisone to 40 mg. of hydrocortisone was followed by a much greater sense of well-being. At the present time she is still edematous, still has to bandage her legs daily, but feels well and is working an eight-hour day as a nurse, and is on an unrestricted diet, in pleasing contrast to the strict sodium restriction enforced during the previous ten years.

COMMENTS

This case poses the problem as to whether this is primary or secondary hyperaldosteronism. The presence of an adenoma does not necessarily imply that hyperaldosteronism is the primary disease and that the edema originated from sodium retention consequent upon the high levels of secretion of aldosterone. The formation of edema as a result of an abnormality of the permeability of this patient's capillaries with respect to proteins, a defect which seems to be well substantiated, may have resulted in secondary hyperaldosteronism, the mechanism of which is at present obscure, and the long continuation of the stimulus to aldosterone secretion may have given rise to the formation of a functioning adenoma.

The degree of sodium retention which has been sustained in this patient over a period of years is remarkable. The earliest determinations of the level of sodium in the urine which are available were made in 1947, two years after the onset of her disease; levels of 2 and 4 mEq./day are recorded on an intake of 48 mEq./day. Nine years later comparable amounts of sodium were being excreted, irrespective of the intake. Although there were considerable day-to-day

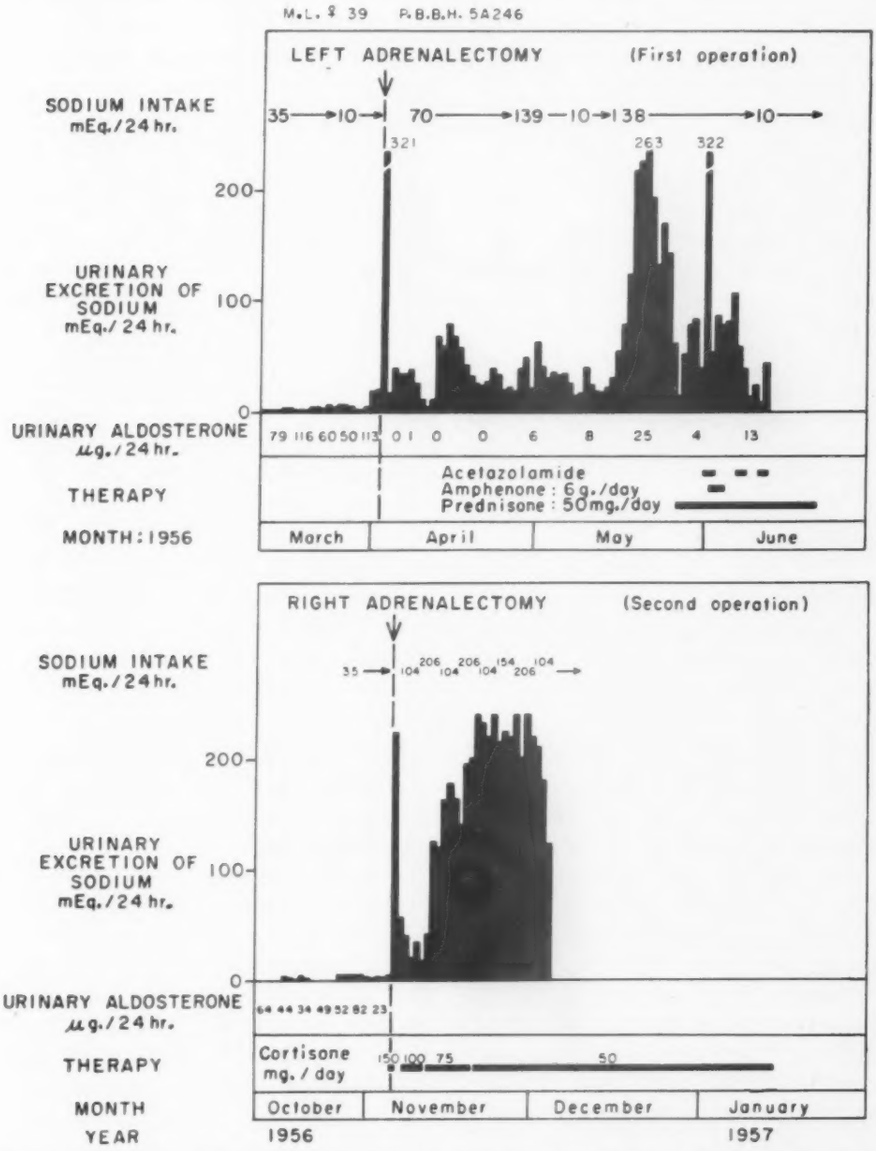

FIG. 9. Comparison of ability to excrete sodium before and after the left adrenalectomy (removal) of adenoma and the right adrenalectomy.

fluctuations in the amount of aldosterone excreted in her urine, fluctuations which may in part be due to imperfections in the measurement of aldosterone in biological fluids, her urinary excretion of sodium rarely exceeded 5 mEq. a day. During the two-month period preceding the second operation it rarely exceeded 1 mEq. a day. There was marked resistance to the action of the many diuretic agents administered, and a satisfactory sodium diuresis was obtained only by the use of an agent which suppresses adrenocortical activity, amphenone, demonstrating the etiological role played by adrenocortical secretion in the genesis of her sodium retention. This case affords an illustration of the usefulness of amphenone in the diagnosis of clinical syndromes due to excessive production of adrenal steroids; it was as a consequence of the uniformity with which a sodium diuresis was produced by amphenone that the decision to explore her adrenal glands was made.

There is a reasonable probability that this patient had been excreting high levels of aldosterone for years. The question arises as to why

TABLE XI
BODY COMPOSITION STUDIES

Data	1951	1953	1957	Normal Values *
Body weight (kg.)	98.2	88.3	76.4	64
Total body water (DHO) (L.)	48.6	.....	33.2	30
Plasma volume (Evans blue) (L)	.....	.....	3.05	2.9
Red cell volume (C^{51}) (L.)	.....	.....	1.91	1.6
Total blood volume (L.)	.....	.....	4.96	4.5
Extracellular volume (thiosulphate space) (L.)	20.0	.....	.....	.....
Extracellular volume (bromide space) (L.)	.....	.....	19.2	15
Total exchangeable sodium (mEq.)	5300	4220	2909	2600
Total exchangeable sodium (mEq./kg.)	54.0	47.8	38.1	41
Extracellular sodium (mEq.)	.....	.....	2640	.....
Residual sodium (mEq.)	.....	.....	269	.....
Total exchangeable potassium (mEq.)	2250	2790	2431	2550
Total exchangeable potassium (mEq./kg.)	22.9	31.6	31.8	40
Extracellular potassium (mEq.)	.....	.....	104	.....
Intracellular potassium (mEq.)	.....	.....	2327	.....
Na_e/K_e ratio	2.36	1.51	1.2	.....
Serum osmolarity (mOsm/L.)	.....	.....	277	.....

* Based on ideal weight for height (65 inches); figures derived from data given by Moore, McMurray, Parker and Magnus [*11*].

this resulted in this case solely in sodium retention and not in the picture of potassium depletion seen in Conn's syndrome, a condition ascribed to prolonged excessive secretion of aldosterone. The administration of aldosterone for short periods (four to six days) to normal subjects and to patients with Addison's disease results in sodium retention and weight gain, with very little change in potassium excretion [*2*]. This is identical with the effects of the short-term administration of deoxycorticosterone. However, as shown by Kuhlman, Ragan, Ferrebee, Atchley and Loeb [*7*] in dogs, the prolonged administration of large doses of deoxycorticosterone results in a syndrome characterized by pitressin-resistant polyuria, periodic muscular weakness, or paralysis due to potassium deficiency, a disease entity closely resembling that described by Conn [*1*]. In the patient under discussion potassium wasting did not occur; this may be due to the fact that she had been on a restricted sodium intake for the duration of her illness. The protective effect of dietary sodium restriction upon the kaliuretic effect of prolonged deoxycorticosterone therapy has been demonstrated in man and animals [*8*].

The observation that in 1948 this patient retained sodium when on a moderate sodium intake but was capable of achieving sodium balance when her intake was raised to 700 mEq. a day suggests to one of us (K. E.) that at that time the mechanism for shutting off aldosterone secretion was operative, but only at very high levels of sodium intake. This is perhaps a pointer to the fact that an adenoma had not yet developed at that date.

Of exceptional interest in this case is the recurrence of hyperaldosteronuria following the first operation. Immediately after the adenoma was removed there ensued a massive diuresis of sodium, the urinary concentration of sodium reaching 122 mEq./L. seven hours after adrenalectomy, contrasting with a concentration of 1 to 2 mEq./L. excreted before operation. Aldosterone could not be demonstrated in the urine on the days immediately following this operation, suggesting that the high level of secretion of aldosterone by the adenoma had effectively suppressed aldosterone formation by the contralateral adrenal despite the presence of a potent stimulus to aldosterone formation, namely, a low salt diet and frequent diuretics. Following removal of the gland containing the adenoma the stimulus to aldosterone secretion was able to act on the remaining adrenal and within three and a half months the secretion of aldosterone had reached such high levels (lower, however, than before the removal of the

adenoma) that sodium was once again virtually absent from the urine. The high level of aldosterone secretion by the adenoma had not, however, suppressed adrenal activity with respect to either 17-hydroxycorticosteroids or 17-ketosteroids, since normal levels of these steroids were excreted in the urine and a normal response to stimulation by ACTH was obtained. In other words, aldosterone at this level of secretion had not suppressed the formation or liberation of ACTH by the pituitary. There is experimental evidence in rats, however, that aldosterone is capable of suppressing ACTH release [*12*].

Edema has persisted in this patient following total adrenalectomy. It is estimated that 10 to 15 L. of edema are still present. It has not been possible to reduce the sodium intake to obtain a satisfactory weight loss without encountering the difficulty of symptoms suggestive of sodium depletion. These symptoms regularly appear when the weight falls to 74 kg. and to date no combination of hormone and salt therapy has been devised which will enable weight loss to continue below this level without the appearance of symptoms. This persistence of edema suggests an etiology other than primary hyperaldosteronism. A vascular abnormality of unknown cause leading to increased permeability of her capillaries is a possible basis, as has been discussed by Emerson and Armstrong [*3*]. This abnormality did not involve the glomeruli, however, since proteinuria was not present. At the present time therapy is directed towards maintaining the patient in sodium balance by means of hydrocortisone, fluorohydrocortisone and a dietary intake of 12 gm. of sodium chloride (205 mEq. Na) in the hope that the vascular lesion will improve in the absence of the aggravating effect on sodium retention of excessive quantities of circulating aldosterone.

Is this then a case of primary or secondary hyperaldosteronism? Whereas the presence of an aldosterone-producing adenoma is in favor of primary hyperaldosteronism, the secondary nature of the hyperaldosteronism, suggested by its association with edema of long duration, was demonstrated by the recurrence of excessive aldosterone formation after the removal of the adenoma. Total adrenalectomy did not cure the patient since she had to be maintained in a state of excessive hydration in order to feel well. The removal of all aldosterone-secreting tissue has not removed the cause of the disease, so that in this respect the disease cannot be classified as primary hyperaldosteronism. The adenoma appears to have been the only adrenal tissue secreting aldosterone despite the presence of a stimulus which presumably acted equally on both glands. Autonomy of the adenoma from control by the stimulus cannot be assumed because aldosterone output appeared to vary with sodium intake. (Tables IV, IX.) When the adenoma was removed and a loss of body water was prompted by vigorous therapy directed at weight reduction, the other gland began to secrete aldosterone. The analogy between this situation and that in which a 17-hydroxycorticoid-secreting adenoma is present with concomitant atrophy of the remainder of the adrenal cortical tissue is apparent. In the present case, however, the stimulus is not the adrenocorticotrophic hormone of the pituitary since 17-hydroxy- and 17-keto-steroids were secreted in normal amounts.

A case similar to that described here has been reported by Mach and colleagues [*9,10*]. Their patient, a forty-one year old woman, had generalized edema with normal serum electrolytes, normal serum proteins, normal blood pressure and no evidence of renal, cardiac or hepatic disease. Elevated levels of aldosterone were present in the urine. Adrenal exploration has not been carried out in this patient.

Note on the determination of aldosterone: The values for aldosterone given in this paper were determined by performing the blue tetrazolium reaction on the eluate from the zone corresponding to the hydrocortisone standards on the Bush "C" system after preliminary chromatography on a florisil column [*13*] and the toluene-propyleneglycol system of Zaffaroni. Following the report by Genest and co-workers [*14*] that this eluate may be contaminated by substances other than aldosterone, a pool of urine from the period before the first adrenalectomy was further examined. The eluate from the Bush "C" system was run on the "E_2B" system of Eberlein and Bongiovanni [*15*]. In addition to aldosterone, a second small spot was present, with running properties faster than aldosterone. This material absorbed ultraviolet light but did not react with blue tetrazolium. It will not, therefore, interfere with the measurement of aldosterone by the method used.

SUMMARY

A case is described of massive edema resulting from a defect of capillary permeability. The resulting secondary hyperaldosteronism was associated with an aldosterone-secreting adrenocortical adenoma. Removal of this adenoma

resulted in temporary disappearance of aldosterone from the urine, accompanied by a sodium diuresis and weight loss. Excessive secretion of aldosterone then commenced in the remaining adrenal gland, with recurrence of sodium retention and weight gain. The removal of this adrenal gland was followed by absence of aldosterone from the urine, sodium diuresis and weight loss. Freedom from edema in this patient has not been achieved owing to the appearance of symptoms suggestive of sodium depletion when her weight falls below a certain level.

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The Developmemt of Myasthenia Gravis after Removal of Thymoma*

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ALTHOUGH there have been numerous contributions to the study of myasthenia gravis, the fundamental etiology and pathogenesis of this condition remain obscure. Indeed, it has been suggested [*1*] that myasthenia gravis represents a symptom complex with the common denominator of neuromuscular block, rather than a single disease. The extreme variability of its manifestations and of the response to treatment lends credence to this hypothesis.

That there is some relationship between the thymus and myasthenia gravis has been known for over fifty years. This was brought into focus in 1939 when Blalock et al. [*2*] published their account of the first thymomectomy in the United States in a patient with myasthenia gravis. Although many thymectomies and thymomectomies have been performed since then, the role of these operations in the treatment of myasthenia gravis and, indeed, the exact nature of the relationship between myasthenia and the thymus remains controversial. Exacerbation of known myasthenia gravis following removal of the thymus or a thymic tumor is well known but the development of myasthenic symptoms for the first time after such an operation is unusual.

The purposes of this communication are: (1) to present a patient who had never had myasthenic symptoms preoperatively but in whom they developed three weeks after complete removal of a thymoma, (2) to review the relationship between the thymus and myasthenia gravis, and (3) to emphasize some important aspects of the diagnosis and treatment of myasthenic and cholinergic crisis.

CASE REPORT

A forty-five year old white man was admitted to the Veterans Administration Hospital, Bronx, New York, in February, 1956, for investigation of a mediastinal mass of five years' duration.

In 1944, calculi had been removed surgically from his left kidney. Postoperatively a rash had developed which involved the skin of most of his body, his oral mucous membrane and his nails. The rash underwent many exacerbations in ensuing years, necessitating multiple hospital admissions. Various fungi had been isolated by culture of the skin lesions at different times, and much local and systemic therapy had been given to the patient without success.

In 1949, a chest x-ray film had been reported as normal. In 1951, a rounded mass in the anterior mediastinum to the left of the midline had been noted. (Figs. 1 and 2.) In the next few years a number of minor surgical procedures had been performed, including hemorrhoidectomy, removal of a rectal polyp, and avulsion of a chronically infected fingernail under brachial plexus block anesthesia.

In 1956, chest roentgenograms revealed that the lobulated mediastinal mass was gradually enlarging and extending to the right of the midline (Figs. 3 and 4), and the patient was admitted to the hospital. No symptoms ascribable to the mass were present. Physical examination revealed extensive Tinea corporis involvement of the trunk, seborrheic dermatitis of the face and scalp, dermatophytosis of the hands and feet, and chronic oral moniliasis. Generalized superficial lymphadenopathy was present, presumably secondary to the skin lesions; biopsy of a right axillary lymph node revealed only chronic lymphadenitis.

Laboratory investigation was not helpful in determining the etiology of the mediastinal mass. Skin tests with tuberculin and the usual fungal antigens were negative. All skin cultures, and one gastric culture, revealed Candida albicans. An angiocardiogram indicated that the mass was not vascular in origin. Proctoscopy revealed a non-specific proctitis, internal hemorrhoids and an adenomatous polyp; these were believed to be responsible for a mild anemia and occasional blood in the stools. Exploration of the mediastinum was believed to be indicated.

Accordingly, on April 23, 1956, after premedication with demerol® and atropine, the mediastinum was entered through a sternum-splitting incision under sodium pentothal, cyclopropane and ether anesthesia.

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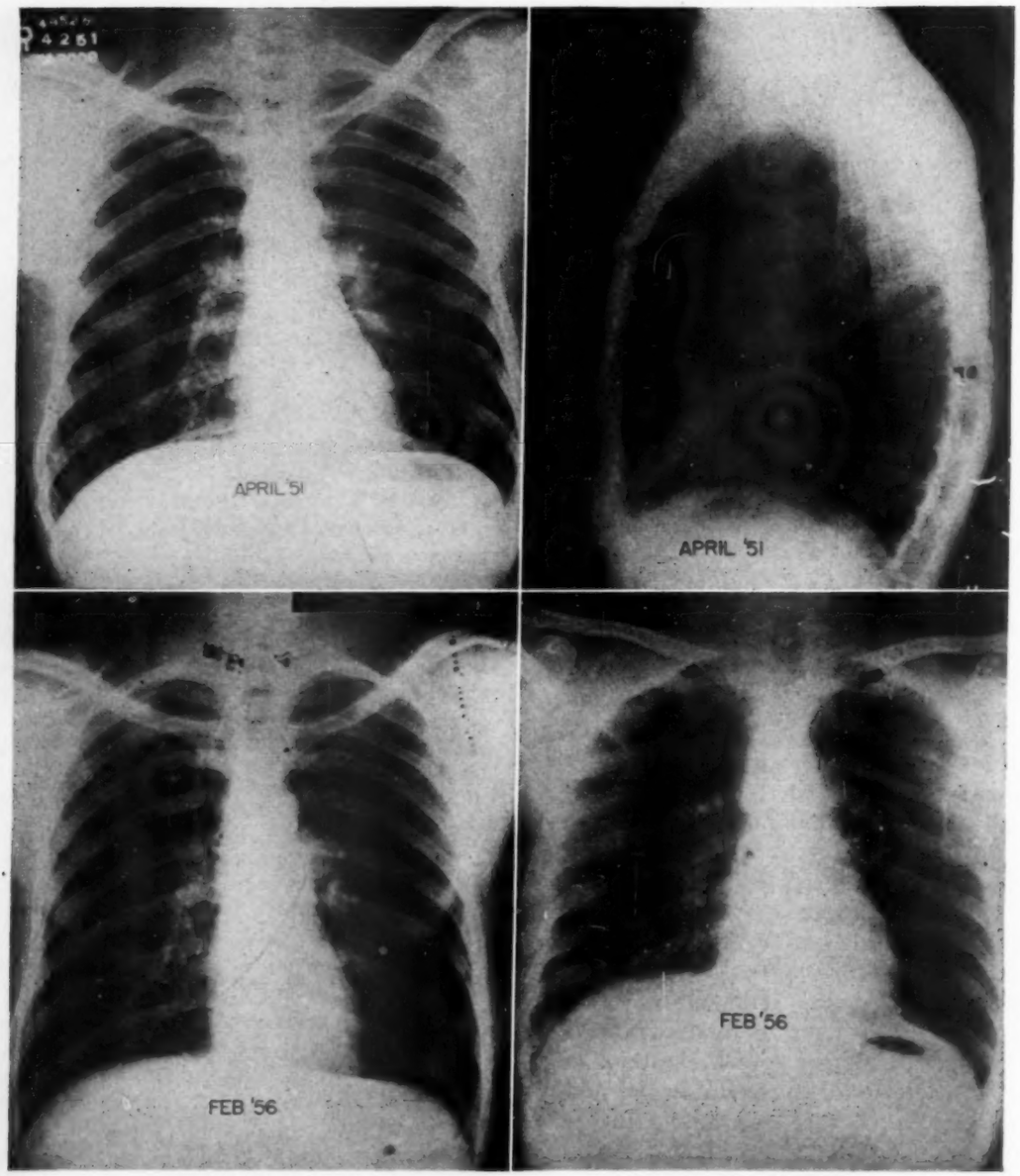

FIG. 1. Posteroanterior view of chest taken in April, 1951. A smooth round shadow is seen below the aortic knob.

FIG. 2. Lateral view of chest taken in April, 1951. The large mass is in the anterior mediastinum.

FIG. 3. Posteroanterior view of chest taken in February, 1956. The mass has increased in size since 1951.

FIG. 4. Lordotic view of chest taken in February, 1956. The mass extends to the right of the midline.

Thirty mg. of succinylcholine chloride (anectine®), given by continuous intravenous drip, were used for skeletal muscle relaxation during the procedure. A tumor mass measuring 7 by 6 by 3.5 cm. was found. It was firm, lobulated, completely circumscribed, and seemed to be encapsulated. It overlay the innominate vein, aorta and upper aspect of the pericardium, and did not involve the sternum, great vessels or pleura. The arterial supply was not identified, but the venous drainage entered the innominate vein from the superior aspect of the tumor. The tumor was completely resected with ease. The histologic diagnosis was "thymoma."

The immediate postoperative course was unremarkable. On the second postoperative day the patient was noted to have retained mucopurulent

secretions and required frequent aspiration of the tracheobronchial tree. X-ray films revealed that a large mediastinal hematoma had developed at the operative site, and that this had drained bilaterally into the pleural cavities. Twelve hundred cc. of bloody fluid was removed from the right side of the chest, and the next morning, 1,000 cc. was removed from the left side of the chest. Multiple bilateral thoracenteses were repeated over the next few days, and by the fourth postoperative day his condition was much improved.

On May 13, the twentieth postoperative day, the patient indicated that he did not feel as well as previously. On May 14, he complained of weakness, feverishness and sweating, although his temperature for the day did not exceed 99°F. On May 15, his weakness had progressed. He also complained of diplopia, drooping of the eyelids, difficulty in swallowing, and respiratory distress when supine. One mg. of neostigmine methylsulfate (prostigmine®) was given intramuscularly on three occasions with no appreciable improvement. A lumbar puncture was entirely normal.

On May 16 further drooping of the eyelids was noted, more so on the left. Diplopia, dysphagia, marked diaphoresis, limited diaphragmatic excursions, tachycardia and severe lassitude were also present. A test dose of prostigmine was repeated without effect. However, 10 mg. of edrophonium chloride (tensilon®) [*3*] was given intravenously, and in one minute the diplopia disappeared, and the ptosis and dysphagia improved. A definite diagnosis of myasthenia gravis was made. One gm. (0.5 cc.) of pyridostigmine bromide (mestinon®) was given intravenously every two minutes, and the strength of the patient's grip was checked with a dynamometer after each injection. He responded maximally with an increase in the dynamometer reading from 16 kilos to 20.5 kilos at a dose level of 3.5 cc. of mestinon, which is equivalent to an oral dose of 210 mg. A total of 11 mg. of mestinon, equivalent to an oral dose of 330 mg., was given during the test, and 210 mg. was prescribed, to be given orally every three hours.

Two hours after the first dose of oral mestinon, however, the patient evinced an increase in respiratory distress, dysphagia and dysarthria, and the dose was then repeated. The favorable effect of mestinon appeared to last for only twenty to thirty minutes, with improvement in strength and lessened sweating during this time. However, abdominal cramps and diarrhea also occurred. The mestinon was repeated four more times during the night, with apparent improvement in the patient's condition, but recurrence of the diarrhea as well, after each dose. The patient received a total dose of 1.8 gm. of mestinon in fourteen hours.

On the morning of May 17 the patient appeared worse, and cyanosis was noted. A tracheotomy was performed, and he was placed in a Drinker-Collins respirator. His regimen consisted of frequent aspirations of the tracheobronchial tree, administration of oxygen, intermittently nebulized epinephrine and alevaire® for bronchodilating effect and liquefaction of secretions, and intravenous fluids. He was later fed by gavage. Erythromycin and gantrisin® were used for antibacterial therapy. Late in the day the patient appeared to have improved, and was temporarily removed from the respirator. However, no intercostal movement was present. Because a tensilon® test (10 mg.) showed definite improvement in intercostal motion and in ptosis, two doses of 0.5 mg. of prostigmine® were given at an interval of four hours, without effect. Further cholinergic medication was withheld, as it was believed that his life-threatening respiratory distress was being well handled by the respirator and adjunctive therapy, and because of the possibility that some of his deterioration had been on the basis of cholinergic overdosage.

Over the next few days his condition remained critical and use of the respirator was continued. Episodes of marked spontaneous diaphoresis were noted. Frequent thorough aspiration of the trachea through the tracheotomy tube was the most important therapeutic measure during this period.

By May 21 some spontaneous intercostal and diaphragmatic motion was noted. During the next few days multiple tests with prostigmine or tensilon were performed with apparent improvement in some functions at times, and either no change or slight worsening of performance of repetitive activity at others. Although no fasciculations were noted, it was decided that respirator therapy should be continued, and cholinergic medication withheld, as error on the side of underdosage rather than overdosage was considered preferable.

By May 31 intercostal motion was much better, the patient could tolerate short periods out of the respirator without undue fatigue, and he was capable of raising his own secretions. On June 18 he was out of the respirator completely, and on June 21 the tracheotomy tube was removed. On June 29 examination revealed slight slurring of speech, no diplopia, some bilateral ptosis which was increased by repetitive blinking, and fatigue on climbing stairs. At this time evidence of genitourinary tract infection became manifest, and was successfully treated. On July 27, two months following the onset of the myasthenic syndrome, examination no longer revealed any evidence whatsoever suggestive of myasthenia gravis, and all functions tested appeared slightly less efficient after a test dose of prostigmine. It was concluded that there was no indication for cholinergic medication.

The patient, when carefully questioned, recalled a transient two-week episode of diplopia fifteen years prior to admission. Blurring of vision in 1949 had been successfully corrected by eyeglasses. There was nothing else in the past history to suggest myasthenia gravis. He was discharged in October after further

dermatologic therapy, and when last seen fifteen months postoperatively had maintained his asymptomatic clinical state.

RELATIONSHIP BETWEEN MYASTHENIA GRAVIS AND THE THYMUS

Although Wilson [*4*] has been able to extract substances from human tumors and fetal whale thymus which can produce myasthenia-like effects, the major evidence of a relationship between myasthenia gravis and the thymus derives from clinical and pathological studies. Some abnormality of the thymus is found in the majority of myasthenic patients. Keynes [*5*] states that unless a tumor is present the thymus is normal in size in myasthenia gravis, and others agree [*6*]; but although Castleman found no gross abnormalities in a large series [*7,8*], microscopic changes, usually consisting of the presence of numerous medullary germinal centers, were noted in 80 per cent of the non-neoplastic thymuses. These germinal center changes, interestingly enough, are found in the otherwise normal thymic remnants in patients who have thymomas associated with their myasthenia gravis.

Strong evidence of a relationship, albeit an obscure one, stems from the multiple reports of remissions in myasthenia gravis following resection of non-neoplastic thymus glands. Keynes' work [*9*], and that of Ross [*10*] indicated that 60 to 70 per cent of myasthenic patients were considerably improved following resection of the thymus. Schwab and Leland [*11*] state that thymectomy is the therapy of choice for myasthenia gravis in women under thirty without thymomas, especially if the disease is of less than five years' duration. Many observers have noted a high incidence of remissions in the natural course of myasthenia gravis, but Viets [*12*] believes that no other therapy has such a favorable rate of remission, and considers his results with thymectomy to be excellent in 40 per cent of his patients, and good in an additional 25 per cent. He does not believe that patients over the age of fifty, or under the age of five, or those who are well adjusted on small doses of neostigmine are suitable for the operation. The Hopkins group [*13,14*] states that thymectomy probably gives the best long-term results in the treatment of myasthenia; whereas observers at the Mayo clinic, after some initial feeling that thymectomy did not increase the incidence of remissions [*15,16*], have concluded that the procedure is of value in females [*17*]. Osserman [*1*] agrees that thymectomy is indicated in females with severe disease.

A definite relationship also appears to exist between myasthenia gravis and thymomas. Some opinion has been expressed that these tumors are almost invariably associated with myasthenia gravis [*18*], but many cases of thymoma are known in which myasthenia was not present preoperatively, and did not develop during the period of postoperative follow-up. The incidence varies considerably from series to series, as might be expected from the relatively small number of cases seen by any one group. For example, in nineteen cases of thymoma Effler [*19*] reports only six instances of myasthenia; whereas Seybold et al. [*20*] noted myasthenia gravis in thirty-four of forty-five patients with proved thymomas, an incidence of seventy-five per cent. A similar figure was given by Mendelow [*21*] in a recent discussion of the subject. On the other hand, most authors agree on the opposite relationship, that is, that the incidence of thymic tumor in patients with myasthenia gravis is 15 per cent [*5,7,9,17,20*]. Cases of remissions in myasthenia gravis following excision of a thymoma have been reported [*22,23*], but most observers agree that when a thymoma is present the myasthenia tends to be more severe, and the results of excisional surgery are poor [*5,14,16*] and not uniform [*20*]. In fact, Keynes [*9*] points out that in some series in which poor results have been reported in myasthenia gravis following thymectomy the patients with thymomas, who could be expected to do poorly, were not separated from those without neoplasms. Eaton [*17*] confirms the poor prognosis in patients with thymomas, but states that females with tumor may be benefited by excision.

The subject is further complicated by lack of agreement on the histological classification of thymomas, and on the criteria of malignancy in them. Seybold [*20*] indicates that histological criteria alone do not differentiate the thymomas which are localized from those which are invasive; and Keynes [*5*] states that thymomas are "malignant" in spite of the histological picture when the tumors infiltrate surrounding tissues or become intimately attached to them by fibrosis. It has been stated [*23*] that myasthenia gravis is rarely associated with "malignant" thymoma; Seybold [*20*] thinks this may be partially due to incorrect interpretation of the histology in certain cases, and Morgan and Dudley [*24*], in a review of the literature, men-

tion thirty-seven cases of malignant thymoma in which thirty patients had myasthenia gravis. In addition, attempts have been made to distinguish between thymomas which are associated with myasthenia gravis and those which are not, on the basis of histological characteristics such as the relative preponderance of large or spindle-shaped epithelial cells. Ehrenreich and Allen [*25*], in a study of the patient reported in this paper, think that the tumor was most probably of the "non-myasthenic" type, although they indicated that grounds for differentiation are shaky. Castleman [*7*], in a discussion of this problem, concluded that there were no foolproof histological criteria on which to base a differentiation.

Various temporal and clinical situations involving myasthenia gravis and thymomas have been described, with little clarification of the nature of the relationship. Keynes [*5*] suggests that thymomas are often present long before the onset of myasthenia gravis, and describes a patient with myasthenic symptoms for only three months who had a large calcified tumor at autopsy. Effler [*19*] mentions a patient treated with radiation therapy in whom a thymoma had been diagnosed at thoracotomy but not excised, myasthenia gravis developing two and one-half years later; the case of Derow et al. [*26*] was quite similar; Morgan and Dudley's [*24*] patient had a known inoperable thymoma for seven years before severe myasthenia developed, and in Levine's [*27*] case myasthenia gravis developed while the patient was undergoing radiation therapy to a mediastinal mass which proved to be a thymoma at postmortem examination. Eaton [*16*] describes the unusual case of a patient with severe myasthenia and a small mediastinal tumor; twelve years later the myasthenic symptoms were minimal, and the tumor had greatly enlarged. As mentioned earlier, remission in myasthenia gravis can occur following thymomectomy; but it is well known that severe exacerbations of the disease can also occur during the immediate postoperative period, and many such patients have been described [*5,15,19*]. It is possible that the non-specific stress of the operative procedure rather than the removal of the thymoma *per se* is responsible for the exacerbation in these patients, as Schwab and Leland [*11*] point out that other surgical procedures, fractures, accidents and various emotional stresses are frequently associated with worsening of myasthenia. Keynes [*5*] has found that his patients with thymoma do better when a course of radiation therapy, as described by Williams [*28*], is given first, and is later followed with excisional therapy; and Osserman, after a lengthy review of the problem [*1*], agrees that this is the treatment of choice for thymoma associated with myasthenia gravis.

In recent years a number of instances of onset of myasthenia gravis following partial or complete removal of a thymoma from the mediastinum, when no myasthenia had been present preoperatively, have been reported. Fershtand and Shaw [*29*] described a twenty-seven year old man who had a resection of a large mediastinal mass which had produced superior vena caval compression. Myasthenia gravis developed immediately postoperatively, and was so diagnosed on the second postoperative day. The patient responded to prostigmine therapy. It should be noted that resection of the entire tumor was not possible at the time of surgery, and that the patient died of cardiac involvement by tumor a year later. A similar case in a fifty-one year old man was reported by Fisher and Child [*30*]. Here also some tumor, implanted on the pleural surfaces, was not resectable. Myasthenia gravis developed with the patient still on the operating table, and persisted until his death one month later. The patient had received 10.5 mg. of curare during the operative procedure, and the authors believed that the myasthenic onset may well have been precipitated by the use of this agent [*31*].

Osserman [*1*] refers to two cases in which myasthenia developed postoperatively, and these are described by Mendelow and Genkins [*32*]. One patient, a thirty-seven year old woman, had a malignant thymoma diagnosed at thoracotomy. The tumor was not resected, however, and myasthenia gravis developed one month later. The second patient was given ACTH and radiation therapy to a mediastinal mass which later proved to be a malignant thymoma at thoracotomy. When ACTH was discontinued some time postoperatively, myasthenia gravis developed. The tumor in this case also was not resected.

Ringertz [*33*] mentioned a similar case of incomplete resection and subsequent myasthenia, and Gray [*34*] indicated that he knows of five such patients, although he did not comment upon the completeness of tumor removal.

Unlike the partial resections in the patients described, Rowland et al. [*35*] described two

cases in which thymomas were apparently completely resected. In one patient myasthenia gravis developed a few weeks postoperatively, and at autopsy only hyperplastic thymic remnants, but no tumor, were found. In the other patient myasthenia gravis did not develop until five years following resection of the thymoma.

Strieder [*36*] mentions a patient in whom myasthenia gravis developed two years following excision of a thymoma. A remission was later obtained following resection of remaining normal thymus gland. Similarly, Madonick et al. [*37*] described a thirty-three year old woman in whom myasthenia gravis developed fifteen months following complete resection of a thymoma. In this patient radiation therapy and resection of residual thymic tissue did not favorably affect the myasthenia. Finally, Roe [*38*] has recently described a forty-three year old man in whom not only was an encapsulated thymoma resected but a complete mediastinal dissection also was carried out. Mediastinal connective tissues, including normal thymic remnants, were removed. Myasthenia gravis developed for the first time six weeks later, after an uneventful postoperative course.

In our patient the onset of severe myasthenia gravis occurred twenty-one days after complete resection of an encapsulated thymoma. Succinylcholine (anectine) was used to achieve skeletal muscle relaxation during the operative procedure. Curare, which produces a competitive block in normal muscle, is known to aggravate the symptoms of myasthenia gravis [*31*]; whereas succinylcholine, which produces a depolarizing block [*1*], does not adversely affect myasthenic patients and is, in fact, the agent of choice for skeletal muscle relaxation in them. Because of this and because of the three-week interval between the operation and the onset of the myasthenic syndrome, we believe that the drug played no part in its development in our patient, unlike the result with curare in Fisher and Child's case [*30*]. In addition, we are of the opinion that the difficulty with secretions and ventilation on the second through the fourth postoperative days is easily explained by the large mediastinal hematoma which decompressed itself by drainage into both pleural cavities. Ours, then, would appear to be the sixth reported case in which myasthenia gravis developed for the first time postoperatively in a patient whose thymoma has been completely excised.

The puzzling relationships between myasthenia gravis and the thymus appear on the surface to be confused further by cases of this type, in which a "paradoxical" situation seems to exist. Certainly, if the thymus or a thymic tumor is etiologically related by an endocrine secretion to myasthenia gravis, one should not expect exacerbation of symptoms after removal of the tumor, and still less, for the first manifestations of myasthenia gravis to appear following excision. Experiences of this type therefore only serve to confirm our inability to understand clearly the nature of the relationship.

The thymus is affected in many situations in which the endocrine glands are involved [*6,39*]. Normally, the thymus undergoes considerable involution at the time of puberty, and excision of the gonads will delay this involutional process. Removal of the thyroid will hasten involution of the thymus, and hyperthyroidism in association with myasthenia gravis and thymic hyperplasia is well known, 5 per cent of myasthenic patients having been reported to have hyperthyroidism [*40*]. Recently myxedema has also been reported in conjunction with myasthenia [*41*]. Similar paradoxical relationships with the adrenal gland exist. The involutional effect of adrenal secretion on the thymus is well known, and Castleman [*7*] mentions eight cases of thymic tumor in association with Cushing's syndrome.

Eaton et al. [*16,17*] are of the opinion that a basic endocrine disturbance probably exists which leads to both myasthenia gravis and abnormal changes in the thymus, and that in some way thymic resection can lessen the severity of the myasthenic state. Keynes [*5*] suggests that a silent thymoma may be an inactive phase of a neoplasm which produces myasthenia, but thinks that "even if the thymus gland is responsible for initiating the disease, the process can sometimes still go on, after the responsible agent has been removed, until the abnormality becomes irreversible."

The generally good results from resection of the non-neoplastic thymus in myasthenia gravis, and the specific histological changes, suggest that a close and possibly an etiologic relationship may exist. However, as so many apparently conflicting relationships occur, and although there are difficulties in attempting a conclusion, it seems to us that when myasthenia is associated with a thymoma, no specific parallel relationship between the two has been established. Also, the course of the myasthenia is, in

general, unaffected by what one does to the thymoma: as neither hormonal nor drug therapy, nor radiation, nor surgery, whether before or after myasthenia has developed, alters the severe myasthenic syndrome in the majority of patients. In this sense the initial onset of myasthenia in the immediate postoperative period is probably due to non-specific factors, such as stress, or to the concomitant use of curare; the initial onset of myasthenia some time after excision of the thymoma is unrelated to the surgery *per se*.

MYASTHENIC AND CHOLINERGIC CRISIS

The term crisis has been defined by Tether [*42*] as the failure of muscles concerned with respiration and/or deglutition to such an extent that neither function can be maintained without mechanical aids. In recent years it has been realized that in patients with myasthenia gravis who are being treated with cholinergic drugs two types of crisis may develop: *myasthenic*, when due to a relapse of the syndrome *per se*, or *cholinergic*, when due to overdosage. Mixed forms also occur. Both types of crisis are characterized by profound weakness and abnormal fatigability of the muscles of respiration as well as those innervated by the cranial nerves. In addition, Grob and Harvey [*43*] have classified the symptoms and signs of cholinergic crisis as *muscarinic*, *nicotinic* and *central nervous system* in type. The muscarinic manifestations include increase in salivary, sudorific, lacrimal and bronchial secretions; miosis; anorexia, nausea, abdominal cramps, diarrhea, and incontinence of bowel and bladder; dyspnea, substernal pressure and pulmonary edema. Among the nicotinic symptoms and signs are fasciculations, muscle spasms and weakness. The central nervous system phenomena include anxiety, restlessness, vertigo, headache, confusion, coma and convulsions. Thus the clinical picture may help to differentiate the two types of crisis; there is such close resemblance between them, however, that it may be impossible, on clinical grounds alone, to make this differentiation.

In the case presented here it was difficult to determine on May 17 whether the crisis was myasthenic or cholinergic in type. On the one hand the response to the intravenous administration of tensilon suggested a myasthenic component; on the other hand, several of the symptoms and signs, such as diaphoresis, increased bronchial secretions and muscle cramps, were compatible with the earmarks of cholinergic toxicity. It should be pointed out also that the patient received a large amount (1.8 gm.) of mestinon before the development of this critical condition. It is conceivable that a combined myasthenic and cholinergic crisis existed in this patient.

The importance of trying to differentiate a myasthenic crisis from a cholinergic crisis has been discussed by several investigators [*42–47*]. Since this differentiation is frequently impossible on clinical grounds alone, one should attempt to determine the nature of the crisis by the use of drugs. Tether [*42*] and Wilson et al. [*44*] recommend the use of atropine sulphate intravenously in large doses. Specifically, the former suggests that if excess secretions, miosis or relatively slow pulse are found, atropine 1.2 mg. be given intravenously and repeated frequently as long as these conditions are present. It should be emphasized that although atropine will not relieve cholinergic weakness, it will alleviate most of the muscarinic symptoms. If there is no improvement with atropine a tensilon test is performed according to the method of Osserman and Teng [*47*]. One cc. (10 mg.) of tensilon is placed in a tuberculin syringe; 0.2 cc. of this solution is injected intravenously during a period of fifteen seconds and the needle left in place; if no reaction occurs after thirty seconds the remaining 0.8 cc. is injected. If improvement occurs the crisis is probably myasthenic, and cholinergic therapy is indicated; if fasciculations and/or no improvement follow the injection of tensilon the crisis is probably of cholinergic type.

If there is an inadequate response to drug therapy it should not be difficult to decide when to place a patient in the respirator. We agree with Rowland et al. [*35*] that absolute criteria, such as a critical value of the vital capacity, are not particularly useful. The respiratory excursions and the ability to clear secretions are the principal factors to be considered. If there is any doubt whether mechanical aid is necessary, the respirator should be used. Harvey [*48*] stresses the early use of the respirator before respiratory insufficiency of a severe degree has developed.

We believe, furthermore, that a tracheotomy should be performed on every myasthenic patient who needs treatment in the respirator. Korey and Randt [*45,46*] and Rowland et al. [*35*] advocate this procedure. Without a tracheotomy it is impossible to improve tracheobronchial

secretions adequately, and retained secretions and bronchopneumonia are as much a threat to life as the paralysis of respiratory muscles. The importance of frequent suctioning of the tracheobronchial tree through the tracheotomy tube cannot be overemphasized.

The use of atropine may help to reduce secretions but if the patient is receiving cholinergic drugs, the masking effect of atropine on the symptoms of early cholinergic overdosage, which has been discussed by Schwab [*49*], should be borne in mind. If it has been established that the crisis is of the cholinergic type, however, atropine is definitely indicated, for Grob and Harvey [*43*] and Grob et al. [*53*] have pointed out that the patient in a cholinergic crisis tolerates and requires massive doses of atropine. As additional measures the inhalation of bronchodilators, such as aqueous epinephrine 1:100, and detergents, such as alevaire,® through the tracheotomy tube has proved to be of considerable value in maintaining a patent airway and facilitating removal of secretions. The judicious delivery of oxygen through the tube is also indicated.

Several other supportive measures deserve mention. The fluid intake and output must be measured and the electrolyte status determined at appropriate intervals. Since the patient in the respirator usually has dysphagia and there is danger of aspiration of food and fluids administered orally, it is advisable to maintain nutrition by intravenous infusions during the first few days. If protracted treatment in the respirator is required, a nasogastric tube should be inserted, through which small, frequent feedings may be supplied. Catheterization or condom drainage may be necessary if the patient is unable to control bladder function. As soon as the patient enters the respirator, antibiotics should be given intramuscularly to prevent the development of respiratory tract infection. Demerol and barbiturates may be used to alleviate discomfort and anxiety [*42*], but morphine should not be given since cholinergic drugs are said to potentiate its action [*43*].

The question whether or not cholinergic drugs should be used in treating a myasthenic crisis after the patient has been placed in a respirator is controversial. Tether [*42*] recommends that cholinergic therapy be varied with the needs of the patient and guided by tensilon tests. He further states that if there is any doubt concerning the type of crisis, it is far better to underdose than to overdose. He considers mestinon® to be the drug of choice because it has less pronounced muscarinic effects. Rowland et al. [*35*] believe that when a patient who is receiving large amounts of neostigmine is placed in a respirator the dose should be reduced. They add that there is not sufficient evidence to conclude that neostigmine should be completely withdrawn from every respirator patient, and that it may be advantageous to continue the drug in amounts sufficient to insure cooperation, communication, coughing and swallowing. It is interesting to observe that these authors [*35*] question the modern concept that in clinical situations overdosage can cause neuromuscular block, thus increasing weakness. Gammon [*50*] advises that the patient with a myasthenic crisis usually requires much smaller doses of the drug while in a respirator. Osserman and Teng [*47*] state that if a patient in crisis is placed in a respirator it is advisable to discontinue cholinergic medication for the first twenty-four hours. Their rationale for this method is that if the crisis is cholinergic the effects of medication will wear off during this period of time; if the crisis is myasthenic, omission of the drug may possibly lower resistance to the drug when it is reinstituted. When drug therapy is resumed they assess its efficacy by means of tensilon tests. Korey and Randt [*45*] present some cogent reasons for withholding cholinergic drugs in the myasthenic crisis which does not respond to neostigmine and which requires respirator therapy.

Several authors have expressed their views on the drug therapy of crisis without particular reference to whether the patient is in or out of the respirator. Thus in 1947 Eaton [*51*] maintained that the administration of too much neostigmine in crisis is an error which is less likely to be made than the error of not giving enough neostigmine. Yet he did state "Increase of the dosage of neostigmine may lead to increased production of thick saliva. Thus the patient fails to obtain relief with greater dosage." Harvey [*48*] states, "In a very severe myasthenic it is difficult to give too much neostigmine as long as atropine in adequate amounts is administered with it." Both of the aforementioned authors recommend the early use of the respirator. Viets [*52*] regards overdosage with neostigmine as the most frequent emergency, which he thinks can be recognized by the characteristic symptoms, especially diarrhea. For this situation he recommends reduction in neostigmine

intake and the administration of atropine. For the treatment of respiratory embarrassment without the other symptoms he advocates an increase in cholinergic drugs.

From this brief review of the literature it is observed that there is some difference of opinion concerning the treatment of myasthenic crisis. Most of those who recommend continuing cholinergic drugs after the patient has been placed in the respirator agree that the dosage should be reduced. The question whether or not omitting the drugs for a while increases their responsiveness when they are later resumed remains unanswered. It is impossible to say whether or not the patient presented in this report would have had a remission sooner if cholinergic drugs had been administered while he was in the respirator. In view of his continued improvement, however, it was deemed advisable to allow a natural remission to take place, and he has subsequently done well without medication. Although others [*45*] have reported treating some patients by this method, it is obvious that no conclusions can be drawn from so few cases. Since this is a moot point, it might be helpful if those who treat large numbers of myasthenic patients would report their experiences in detail. In our opinion the most important aspects of therapy consist of maintenance of a patent airway and continued artificial respiration. If there is doubt regarding the type of crisis it is advisable to perform a tracheotomy, place the patient in a respirator and withhold cholinergic drugs.

SUMMARY

The case of a patient in whom symptoms of myasthenia gravis developed three weeks after complete removal of a thymoma is described. In this patient a state of crisis developed, for which he was successfully treated in a respirator. Thus far he has remained asymptomatic without the use of cholinergic drugs.

On review of the literature it has been found that various temporal relationships between myasthenia gravis and thymic tumor have been observed. The nature of these relationships remains obscure.

The differential diagnosis and treatment of myasthenic and cholinergic crisis is discussed. The controversial nature of the management of such cases reflects an incomplete understanding of the pathophysiology of myasthenia gravis. There is need for detailed reports of the treatment of crisis by those investigators to whom large series of cases are available for study.

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An Hereditary Anemia with Hemochromatosis*

Studies of an Unusual Hemopathic Syndrome Resembling Thalassemia

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RECENTLY the authors observed two brothers who demonstrated a refractory anemia similar in many respects to Mediterranean anemia. One of the brothers, O. M., has a severe anemia and has to date spent the past eighteen months as a patient in this hospital. The other brother, H. M., has never been hospitalized and, aside from a mild hypochromic anemia, appears to be in good health. The brothers are descended from Swiss-English-German stock.

O. M., the brother with the severe anemia, has been studied in great detail. We have obtained basic hematological data from members of the immediate family which indicate that the mother and the sister of our patient may be carriers of the defect. It was apparent that we were not dealing with hereditary elliptocytosis, hereditary spherocytic disease or with the hereditary non-spherocytic anemia described by Crosby [*1*]. The rather uniform morphological characteristics of the red blood cells in these syndromes and the unique alteration in structural stability of the red cells which are the distinguishing features of these anemias were not apparent in the family under consideration [*1–3*].

CASE REPORT

The patient was a thirty-three year old self-employed white man who was first admitted to the Fresno Veterans Administration Hospital on August 17, 1955, with a referral diagnosis of "possible subacute bacterial endocarditis." For the preceding six months he had noted increasing fatigue and pallor of his skin. For one month prior to admission he had been under the care of a private physician and had been taking 1 gm. of ferrous sulphate daily. In June, 1955, he had undergone a fairly extensive diagnostic workup by a local internist and was found to have a moderate anemia with a hemoglobin of 9.65 gm. per cent and a red blood cell count of 4.79 million per cu. mm. Blood smears had shown hypochromic red blood cells with marked anisocytosis and poikilocytosis. Bone marrow smears showed marked normoblastic hyperplasia with a myeloid-erythroid ratio of 1:1.5, and note was made of splenomegaly and a rough, loud systolic heart murmur.

The patient had no history of having had rheumatic fever. He had served in the armed forces from 1944 to 1946 and his attention had never been called to the presence of a heart murmur or anemia. He recalled, however, that since childhood he had always been somewhat pale and underweight. His brother has a mild anemia and in the past had received hematinics which seemed to have no effect. The patient's father died of a brain tumor in 1955; the mother is living and in apparent good health. The patient gave no history of exposure to hemolytic agents or to bone marrow depressants.

Physical examination revealed a fairly well developed white man with moderate pallor of the skin and mucous membranes. There was no evidence of petechiae nor of any significant adenopathy. The pulse was regular at 100 per minute and the blood pressure was 120/80 mm. Hg. The oral temperature was 99.5°F. The lungs were clear to percussion and auscultation, and cardiac enlargement was not apparent. The heart rhythm was regular and a grade 3 harsh systolic murmur was heard along the left sternal border, loudest in the 2nd intercostal space. The intensity of the murmur varied considerably with different phases of respiration; forced expiration almost completely extinguished the murmur. The abdomen was scaphoid and non-tender. The area of liver dullness was increased but the liver edge could not be palpated. The spleen was easily palpable and firm, with the edge about 6 cm. below the left costal margin. The remainder of the physical examination was entirely within normal limits.

The hemoglobin was 9.0 gm. per cent, the hemato-

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crit 36 per cent and the red blood cell count 4.94 million per cu. mm. The white blood cell count was 5400 per cu. mm. with 34 per cent neutrophilic granulocytes, 63 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The urinalysis showed an occasional white blood cell in the sediment. The serological test for syphilis was negative. The blood non-protein nitrogen was 25 mg. per cent. The anti-streptolysin titer was positive 1:125. The platelet count [*4*] was 162,000 per cu. mm. (normal 150,000 to 300,000 per cu. mm.); a red blood cell fragility test showed beginning hemolysis at 0.48 per cent saline and complete hemolysis at 0.27 per cent saline. The serum proteins totaled 7.5 gm. per cent with 5.1 gm. of albumin and 2.4 gm. of globulin. Seven successive blood cultures were all negative. The direct and indirect Coombs' tests were negative. Bone marrow smears and aspiration biopsy showed striking normoblastic hyperplasia. Tissue sections from a needle biopsy of the liver showed moderate hemosiderosis and some portal fibrosis. A chest x-ray showed clear lung fields and no cardiac enlargement. Fluoroscopy of the chest and x-rays of the skull showed no abnormalities. A plain film of the abdomen demonstrated a markedly enlarged liver and a moderately enlarged spleen. An electrocardiogram showed a normal pattern.

Even though the possibility of bacterial endocarditis was considered to be unlikely, the patient was given a four-week course of penicillin and streptomycin therapy after blood cultures were obtained. He also received 5 units of red blood cell mass and on October 3, 1955, the hemoglobin had risen to 12.3 gm. per cent. During this time no significant change was noted in his clinical status.

From October, 1955, through the middle of February, 1956, the patient showed an anemia of increasing severity. Beginning in the middle of November he had an almost daily temperature rise, at times as high as 103°F. His appetite failed, a painful, generalized urticarial eruption developed which lasted for several weeks, and he complained of vague migratory arthralgia and drenching night sweats. During this period there was no change in the quality or intensity of the heart murmur nor was there evidence of cardiac enlargement. An electrocardiogram taken on February 7, 1956, showed a change from the previous normal, with the appearance of high voltage over the precordium and low T waves in leads I, V-5 and V-6. The T wave was inverted in aVL. The patient had a persistent leukocytosis and a hemoglobin averaging 6.5 gm. per cent from December, 1955, through the middle of February, 1956. A trial of cortisone therapy from January 17, 1956, through February 23, 1956, failed to ameliorate the symptoms, and there was no significant reticulocyte response or rise in hemoglobin. (Fig. 1.) Because of the refractory anemia, together with evidence of a hyperplastic bone marrow and marked erythropoietic activity, it was decided to subject the patient to splenectomy. The day before surgery a splenic needle aspiration was performed and smears of this material showed no evidence of hematopoietic activity. The operation was performed on February 24, 1956, after preoperative preparation with 6 units of whole blood. On the day of surgery the hemoglobin was 14.0 gm. per cent and the hematocrit was 46 per cent. At surgery, a spleen weighing 403 gm. was removed, together with a small accessory spleen found in the main splenic pedicle. Grossly, the spleen was brownish red and a single small area of infarction was found adjacent to the surface. Microscopic sections showed moderate hemosiderosis, some fibrosis, and moderate congestion of the pulp with preservation of Malpighian corpuscles. The postoperative course was completely uneventful and corticoid therapy was gradually withdrawn.

Following a favorable convalescence, during which the patient maintained his hemoglobin at about 14.0 gm. per cent for three weeks, he was given an extended leave of absence on March 15, 1956. He did not return to work but felt quite well until hematuria developed, with left flank pain, in April, 1956, for which he was hospitalized elsewhere. From hospital transfer records and the patient's own statements we were never certain whether the patient had had an acute pyelonephritis or simply a prolonged episode of hematuria. He had passed brown urine loaded with white and red blood cells on several occasions, accompanied by chills and fever. After a week of hospitalization the patient had returned home but stated he did not feel completely well.

He returned to our hospital on May 11, 1956, with the complaint of pain and swelling of several days' duration along the medial aspect of his left leg. On this occasion he had a thrombophlebitis involving the entire length of the left superficial saphenous vein. At this time the hemoglobin was 10.3 gm. per cent, hematocrit was 34 per cent, a white blood cell count was 13,000 per cu. mm. with 63 per cent neutrophilic granulocytes, and the platelet count was 500,000 per cu. mm. He was treated with bedrest and anticoagulants for two weeks and the leg symptoms gradually subsided. Since then he has had repeated episodes of superficial thrombophlebitis of both legs, which have usually been responsive to treatment with phenylbutazone [*5*]. Again his anemia appeared to be refractory although there was some evidence of response to treatment with prednisone during the months of August and September of 1956. (Fig. 2.) During the latter part of October, 1956, large numbers of nucleated red blood cells, as high as 60 per cent of the total nucleated cells, appeared in the blood smears. (Fig. 3.) A leukocytosis developed with a peak white count of 45,650 per cu. mm on October 30, 1956. A bone marrow aspirate showed intense hyperplasia of the entire erythroid series and an increase in reticulum cells.

The patient had at times complained of mild

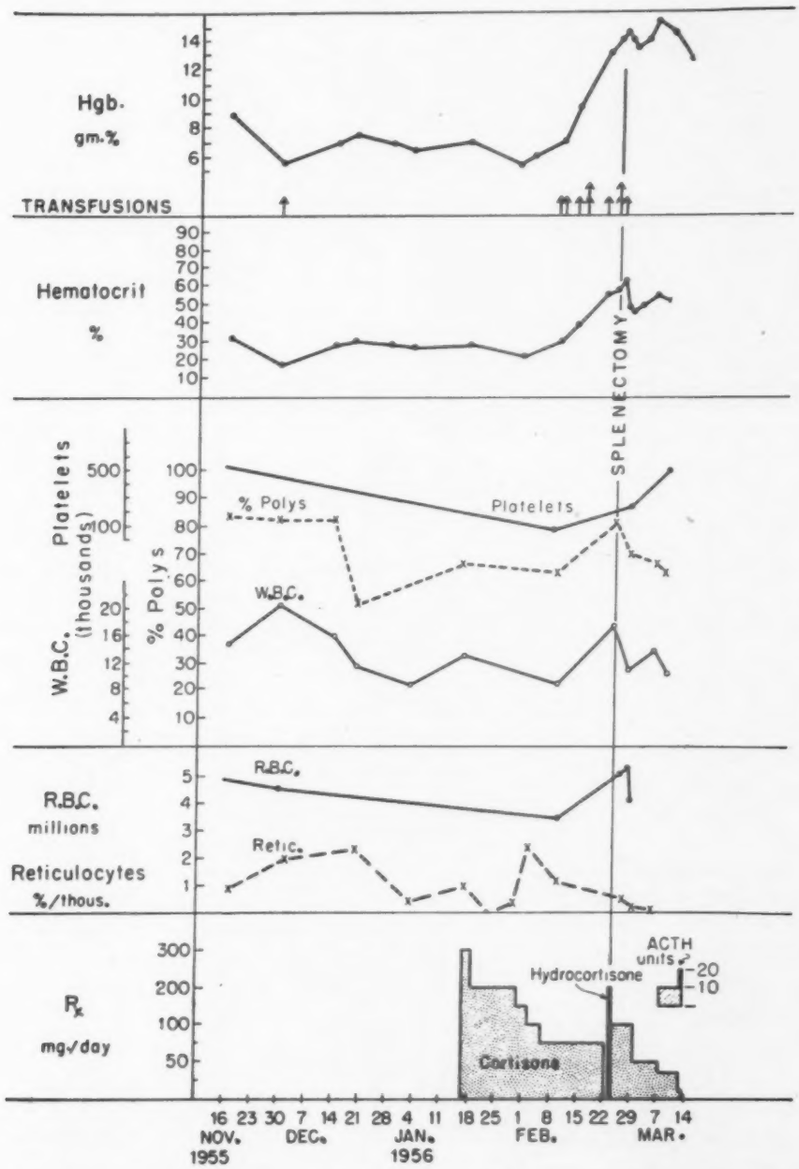

FIG. 1. Hematological changes of patient prior to splenectomy, showing failure of response to the first course of steroid (cortisone) therapy.

epigastric distress, heartburn and dysphagia. During the first course of steroid therapy these symptoms had prompted institution of a bland diet and administration of milk and antacids between meals. On November 7, 1956, while still receiving prednisone, severe generalized abdominal pain and moderate abdominal distention developed, and the patient's temperature rose to 102.5°F. A plain film of the abdomen demonstrated several dilated loops of small bowel distended with gas and fluid. The patient was given 3 units of whole blood and underwent an exploratory laparotomy. A small localized collection of pus was found adjacent to the second portion of the duodenum at the site of a sealed off perforation. The postoperative course was stormy and complicated by a protracted ileus and a wound infection. It was also suspected that the patient had extended the intra-abdominal infection. He was treated intensively with a variety of antibiotics for four weeks during which time he had a continuous low-grade fever with a daily temperature elevation to 100°F. By the end of December, 1956, he had recovered sufficiently to be granted another leave of absence.

He returned to the hospital on January 21, 1957, with a flare-up of his thrombophlebitis. The hemoglobin had declined from a postoperative level of

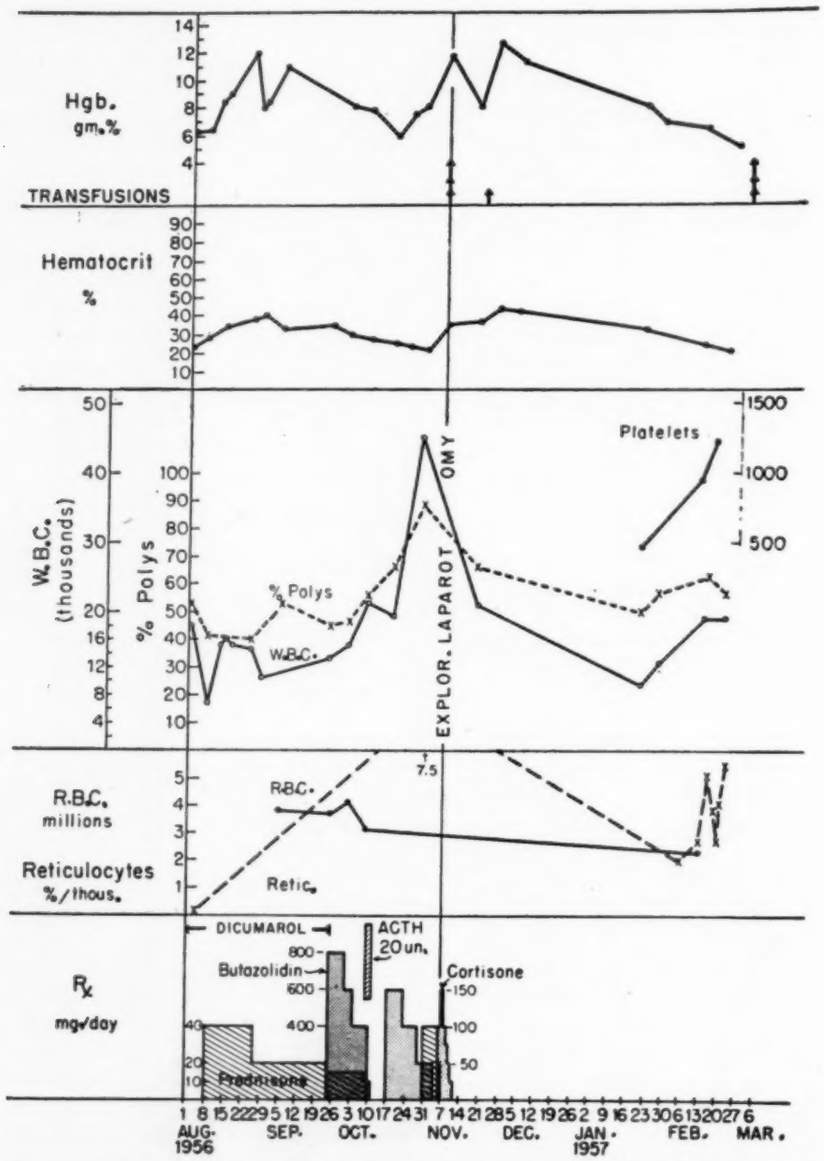

FIG. 2. Hematological changes during and after administration of prednisone.

13.0 gm. per cent to 8.0 gm. per cent and the hematocrit was 33 per cent. There was tenderness, heat and edema along the medial aspect of the right ankle. A striking muddy pigmentation of the skin was noted, particularly over the lower extremities. There was no evidence of cardiac enlargement and the heart murmur was unchanged. Treatment was initiated with phenylbutazone and the pain and swelling of the leg gradually subsided. During February, 1957, large numbers of bizarre platelets had been noted in the blood smears, and on February 15, 1957, the platelet count rose to 1,205,000 per cu. mm. On this date 24 nucleated red blood cells per 100 white cells were also demonstrated in the blood smear.

In February, 1956, the patient was started on a course of oral liver extract (Squibb) providing 30 units daily. Although there was some initial elevation of the reticulocyte count, after three weeks of therapy there was no significant rise in hemoglobin. The patient also did not respond to a course of massive doses of B_{12}. In June, 1957, he was given pyridoxine for eighteen days, 200 mg. daily. There was no significant reticulocyte or hemoglobin response.

ADDITIONAL STUDIES ON O. M.

Since October, 1956, successive films of the chest have shown definite cardiac enlargement. However, the latest chest x-ray, taken on January 22, 1957, has shown the heart to be of normal size. A cholecystogram and an intravenous pyelogram were normal. A

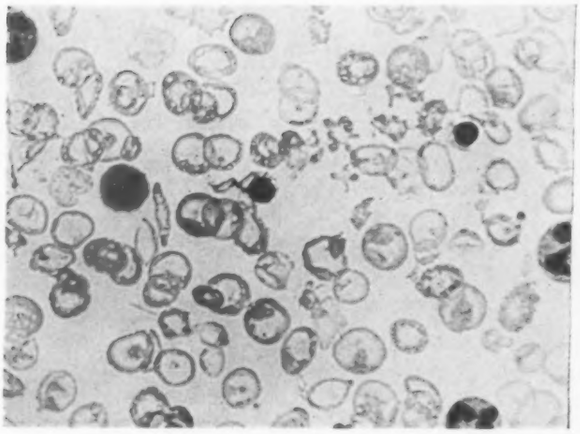

FIG. 3. Blood smear with Wright's stain of patient O. M. showing his usual striking structural alterations of the red blood cells and normoblasts during period of marked erythroid hyperplasia.

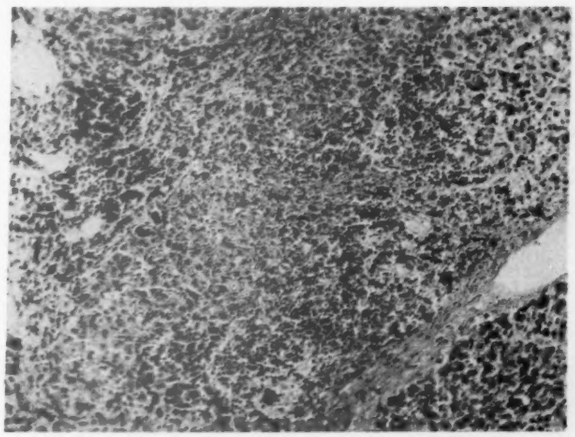

FIG. 4. Biopsy specimen of the liver obtained on November, 1956, showing extensive deposits of hemosiderin and fibrosis. Hematoxylin and eosin, original magnification × 150.

bone survey, made in August, 1956, demonstrated minimal generalized osteoporosis.

Despite hepatomegaly and definite histological evidence of increasing hepatic fibrosis and hemosiderosis, there have been no gross alterations in liver function. (Chart I.) Successive biopsies of the liver, the first in September, 1955, the second at the time of splenectomy in February, 1956, and the third at the time of laparotomy in November, 1956, have shown progressive pigment deposition and the development of a picture typical of hemochromatosis. (Fig. 4.) Successive glucose tolerance tests have demonstrated the recent appearance of a typical diabetic pattern. (Chart II.) At no time has glycosuria been demonstrated in samples of urine obtained at random.

Serum iron and iron binding capacity on August 17, 1956, were 295 mcg. per cent and 352 mcg. per cent, and on February 5, 1957, were 144 mcg. per cent and 204 mcg. per cent, respectively. By the method used [*6*], the normal iron is 60 to 150 mcg. per cent.

An electrophoretic pattern of the patient's hemoglobin obtained by Dr. H. A. Itano of the National Institute of Health with the Tiselius apparatus revealed only normal adult hemoglobin. The Coombs' test has been negative on all occasions and incomplete antibodies have not been detected by incubation of the patient's red cells with 20 per cent bovine albumin. The acid hemolysin test of Ham has been negative on several occasions, and hemosiderin has never been demonstrated in the urine sediment. Successive estimations of the fecal urobilinogen excretion (Chart III) have suggested the presence of a moderately severe hemolytic disease. Since splenectomy, the

DATE	SERUM BILIRUBIN mg.% TOTAL	DIRECT	URINE UROBILIN, POSITIVE DILUTION	BROMSULFALEIN RETENTION 45 min.	CEPHALIN-CHOLEST. FLOCCULA'N 48 hr.	THYMOL TURBIDITY clinical units	SERUM TOTALS gms.% PROTEIN	ALBUMIN	GLOBULIN
8-23-55							7.50	5.10	2.40
9-13-55				5%					
9-27-55	0.85	0.50	+1:80						
11-17-55			+1:40						
2- 9-56				2%			7.40	4.50	2.90
2-14-56					0	1.75			
5-15-56	0.60								
8- 2-56							9.0	5.25	3.75
10-2-56				2.5%	1+				
11-1-56							6.80	4.30	2.50
11-6-56						2.75			
1-22-57				1.5%					

CHART I. Liver function studies on patient O. M. over an eighteen-month period.

patient's red cells have shown increased resistance to hypotonic saline solution (Fig. 5, Chart IV), and on two occasions the mechanical fragility of the patient's red cells was within normal limits. Blood smears stained for iron in April, 1957, revealed the patient to have 20 to 25 per cent siderocytes.

On April 26, 1956, while recovering from a phlebitis, a platelet count of the peripheral blood was 2,700,000 per cu. mm. and in the marrow on the same date an estimate of 3,000,000 platelets per cu. mm. was made. Clumping of platelets was conspicuous in all preparations of marrow and peripheral blood and accurate counting was impossible. The buffy coat of the peripheral blood was 7 mm. and a smear of it showed almost all platelets. The marrow on the same day had a total nucleated element of 119,750 per cu. mm. and 84 megakaryocytes per cu. mm. [7]. The unusually high platelet count was not associated with any specific complaint.

DATE	F.B.S. mg.%	½ HR.	1 HR.	2 HR.	3 HR.	4 HR.	5 HR.
9-28-55	80	160	150	100	85	68	88
2-15-57	111	200	245	245	206		
3-8-57	91	224	264	173	111		

CHART II. Glucose tolerance curve over a period of seventeen months, showing progressive changes to a diabetic pattern.

DATE	STOOL gms.wt.	AVERAGE 24-HR. QUANTITATIVE U.B. mg.	Hgb. NEAREST DETERMINATN	TRANSFUSIONS UNITS	TRANSFUSIONS TIME ELAPSED
9-20-55	337	298.4	7.8	—	—
11-25-55	399	369.0	9.0	2	4 wks.
12-22-55	534	362.0	7.5	1	6 wks.
2-19-56	370	80.0	13.0	5	10 days
6-18-56	430	93.1	11.8	1	2 wks.
1-7-57	327	507.0	11.8	4	9 wks.

CHART III. Fecal urobilinogen studies demonstrating periodic elevations, with coincident hemoglobin determinations and the relation to transfusions.

Red cell survival studies using Cr^{51} [8] were performed on the patient and his brother (H. M.) between May and June, 1957. It was found that the patient's own cells had a shortened life span (nineteen and a half days), while a donor's blood had a normal survival in the patient (thirty-five days). Results of studies on the patient's brother will be discussed subsequently.

Blood typing classified the patient as A_2B; M. N.; $R_1r\left(\frac{CDe}{cde}\right)$. We have typed the mother as A_1B; M. and her blood agglutinates with anti-D, anti-E and anti-c. It does not agglutinate with anti-C. The brother (H. M.) types out group B; M. N. He agglutinates with anti-D anti-C, anti-E and anti-c.

STUDIES ON OTHER MEMBERS OF THE FAMILY

Brother (*H. M.*). This is a thirty-nine year old man who had been known to be anemic for several years.

DATE	PATIENT HEMOLYSIS BEGINS	PATIENT HEMOLYSIS ENDS	CONTROL HEMOLYSIS BEGINS	CONTROL HEMOLYSIS ENDS
8-19-55	0.48 %	0.22 %	—	—
9-8-55	0.44 %	0.32 %	—	—
8-8-56	0.42 %	0.21 %	0.45%	0.30 %
8-30-56	0.39 %	< 0.12 %	0.48 %	0.36 %

CHART IV. Red blood cell osmotic fragility determinations in patient O. M.

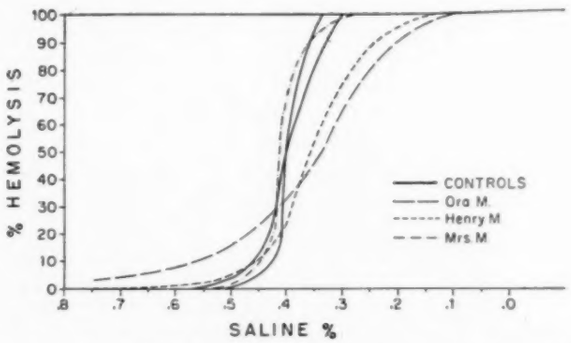

FIG. 5. Red blood cell osmotic fragility curve of patient Ora M., the patient's brother Henry M. and patient's mother Mrs. M. compared with two normal control subjects after patient's splenectomy.

He is currently under the observation of a private physician and has received a variety of hematinic preparations with no apparent effect on his anemia. His history goes back to October, 1955, when at a blood bank he was told that his hemoglobin was too low to qualify him as a donor. At that time his hemoglobin was 9 gm. per cent, and his red blood cell count was 5.3 million per cu. mm. The white blood cell count at that time was 11,200 per cu. mm. He was started at that time on a regimen of multivitamins which later included liver and B_{12}. In spite of all therapy in January, 1956, his hemoglobin was still 9.7 gm. per cent. The red cell count was unchanged. Despite the anemia the patient complained of only mild fatigue, and carried out strenuous farm work for a number of years. Physical examination revealed the patient to have a somewhat bronze pigmentation of the skin. The spleen was not palpable, the liver was palpated 1 fingerbreadth below the right costal margin. His bone marrow examined elsewhere was

	H.A. PATERN'L AUNT	D.C. SISTER	L.M. MOTHER	H.M. BROTHER	W.M. PATERN'L UNCLE
Hemoglobin –gm.%	13.5	12.8	13.0	11.0	15.0
Red blood cells–M/mm³	4.37	5.31	4.58	5.49	4.74
Hematocrit – %	47	48	48	58	47
Mean corpuscular volume – μ^3	107	90.4	105	105.6	99
Mean corpuscular hemoglobin–$\mu\mu$gm.	30.9	24.1	28.6	24.0	31.6
Mean corpuscular hgb.concentrat'n–%	28.9	26.6	27.0	19.0	31.9
Smear	Normal	Slight anisocytosis, poikilocytosis, hypochromasia.	Slight anisocytosis, poikilocytosis, hypochromasia.	Moderate anisocytosis, poikilocytosis, hypochromasia.	Normal

CHART V. Hematological studies in immediate family.

considered to be normal. Bone marrow examination at this hospital in February, 1957, revealed a cellular marrow with evidence of active erythropoiesis and a normal myeloid-erythroid ratio. Blood smears examined in our laboratory on numerous occasions have shown marked variation in size and shape of the red cells, similar to those of our patient, O. M. The platelet count on May 1, 1957, was 500,000 per cu. mm. and on May 9, 1957, was 729,000 per cu. mm. Recently the hemoglobin had ranged around 10 gm. per cent and the hematocrit has varied from 36 per cent to 40 per cent. An osmotic fragility test performed elsewhere on H. M. was reported as normal. Osmotic fragility tests carried out here, however, showed slightly increased resistance, with beginning hemolysis as 0.42 per cent and completed to 0.28 per cent (control was 0.44 per cent to 0.32 per cent); similar results were obtained when the procedure was repeated. (Fig. 5.) The reticulocyte count was 2 per cent; van den Bergh test, direct and indirect Coombs' test, urobilinogen and urine bilirubin were all normal. Serum iron and iron binding capacity were 198 mcg. per cent and 271 mcg. per cent, respectively. Serum iron and iron-binding capacity determinations performed elsewhere several months previously were reported as 234 mcg. per cent and 332 mcg. per cent, respectively. The electrophoretic pattern of the hemoglobin was normal. A red cell survival study showed a normal life span for the patient's own cells. However, Cr^{51} tagged cells of a donor given to the patient had a slightly shortened apparent half life, twenty-three days (normal twenty-five to forty days). Less than 1 per cent siderocytes were present on blood smears.

The brother (H. M.) has three children by his wife of Pennsylvania-Dutch ancestry and all three have had episodes of anemia. A daughter, six years of age, has had anemia from approximately the age of one year at which time the hemoglobin was approximately 9 gm. per cent. In October, 1955, it was 11.2 gm. per cent of hemoglobin and the red blood cell count was 4.2 million per cu. mm. On one occasion the red blood cells were noted to be moderately hypochromic. The red blood cell count in January, 1957, was 4.36 million per cu. mm. with 11.2 gm. per cent of hemoglobin. At that time it was noted that there was a moderate amount of poikilocytosis, slight macrocytosis and hypochromasia and polychromasia.

A son, eight years old, has also had a persistent anemia. In July, 1952, the hemoglobin was 12.6 gm. per cent, with a red blood cell count of 4.4 million per cu. mm. In October, 1955, the hemoglobin was 11.6 gm. per cent and the red blood cell count was 4.45 million per cu. mm. In March, 1956, the hemoglobin was 10.8 gm. per cent with 4.55 million red blood cells per cu. mm. On one occasion the erythrocytes have been reported as being slightly hypochromic.

The third child, a daughter who is four years old and has no particular complaint, also appears to have an anemia; the hemoglobin was reported in March, 1956, to be 10.2 gm. per cent with 4.40 million red blood cells per cu. mm. The smear showed slightly hypochromic red cells.

Sister (D. C.): This thirty-two year old woman is in apparent good health. Her hemoglobin is slightly below normal (Chart v), and her blood smear shows a slight amount of anisocytosis and poikilocytosis with hypochromia of the red cells. No target cells were noted.

Mother (*L. M.*): This sixty year old woman claims good health. Her hemoglobin is slightly below normal, and her red cells have slight variation in size and shape with hypochromia of some of the cells. No target cells were noted. Her serum iron and iron-binding capacity were 126 and 261 mcg. per cent, respectively.

Father (*O. M.*): This man of Scotch-German descent died at the age of fifty-four after a brief illness and was found at autopsy to have a glioblastoma multiforme. He had no history of anemia but laboratory studies during his final hospitalization were reported as follows: Hemoglobin 12.6 gm. per cent, red blood cell count 3.87 million per cu. mm., white blood cell count 6,500 with 68 per cent neutrophilic granulocytes. There was no indication of unusual red cell morphology. No enlargement of the spleen or the liver was observed at the time of autopsy. Sections of brain were obtained and examined. There were areas of well preserved red blood cells which had no apparent abnormalities.

Paternal Aunt (*H. A.*): This fifty-six year old woman was interviewed and found to have no history of anemia. Hematologic studies including blood smears were normal. (Chart v.)

Paternal Uncle (*W. M.*): This fifty-one year old man is in excellent health and has no obvious hematologic abnormalities. Blood smears are normal.

Maternal Uncle (*H. B.*): This man of sixty-eight years is not available for interview or examination, but is reputedly in good health with no history of anemia.

Maternal Grandmother (*T. B.*): This woman died at the age of eighty-five of far-advanced pulmonary tuberculosis. No autopsy was performed but data are available to indicate she was anemic. The hemoglobin estimated eleven years before death (August, 1936) was 65 per cent and the red blood cell count was 3.16 million per cu. mm. In January, 1938, hemoglobin was 80 per cent and the red cells 3.96 million per cu. mm. During her terminal illness, the hemoglobin was 10.5 gm. per cent and the red blood cell count was 3.82 million per cu. mm. with a hematocrit of 40 per cent. On all of these occasions the red cells were reported as normal on the smears. The spleen was not palpable on several examinations.

Maternal Uncle: The patient's mother relates that she had a brother who died at the age of twenty-nine with a diagnosis of "pernicious anemia." No medical data are available on this man.

Maternal Aunt: A younger sister of the mother died at the age of fifteen in England and apparently had been known to be anemic for several years before death. She was also observed to have poor wound healing.

COMMENT

Both the patient and his brother present an unusual type of anemia which is characterized by malformation and increased osmotic resistance of the red cells. In the patient there is no evidence of an autoimmune hemolytic system and there is no reason to believe that such exists in the brother. In terms of red cell osmotic resistance and red cell morphology the disorder in the patient resembles a severe or perhaps intermediate thalassemic syndrome, while the brother might be classed as a so-called thalassemia minor [*9,10*]. The moderately severe type of thalassemia has been reported in adults, typically of Italian ancestry [*11,12*] with characteristic bone changes [*13*] and peculiar physiognomy of the disease. It has become well established that there are hemopathic syndromes associated with the presence of hemoglobin C and E [*14–18*], which are characterized by striking morphological abnormalities of the erythrocyte. Inasmuch as our patient and his brother are of combined Swiss-English-German descent and have not demonstrated the presence of abnormal hemoglobins, there is only a superficial resemblance to these hematological defects. In the moderately severe or severe thalassemic syndrome one should be able to demonstrate significant amounts of alkali-resistant or fetal hemoglobin in the blood of the patient [*18*], and both parents of the patient with severe thalassemia should manifest at least microcytosis or leptocytosis in the peripheral blood. In the cases under consideration neither of these requisites are present.

Within the last twelve years there have appeared a few reports of a peculiar, familial, thalassemic-like disease, presumed to be sex-linked, transmitted through unaffected females and presenting only in males. In 1945 Cooley [*19*] described a familial anemia affecting nineteen of twenty-nine males in five generations. Hematologic studies of two siblings were presented in some detail and, although the anemia was classified as an "elliptocytosis," it is evident from the photomicrographs and further comment by the author that the red cell morphology was primarily that of marked anisocytosis, poikilocytosis and hypochromasia. In addition, in both siblings there was a suggestion from the photomicrographs that there were two basic red cell populations: one characterized by markedly hypochromic cells, some with bizarre shape and many showing considerable variation in size, while the other red cell population appeared to be made up of cells of rather uniform size and deeply stained, resembling spherocytes. Osmotic fragility studies in one of the siblings indicated a wide resistance span, with hemolysis

beginning at 0.48 per cent saline solution and complete at 0.20 per cent saline solution, and a serum iron of 246 mcg. per cent. Splenectomy was performed on this patient; the organ weighed 336 gm., and histologically indicated extramedullary hematopoiesis. There appeared to be some improvement in the patient after splenectomy with a gradual rise in hemoglobin from 5.4 gm. per cent to an average of 11.0 gm. per cent.

In 1946 Rundles and Falls [*20*] presented a study of two families in which a total of four males manifested moderate to severe anemia. These families were traced through several generations and a rather large number of females were found to have minor abnormalities in red cell morphology. Splenomegaly was apparent in all the anemic subjects and a number of others, both male and female, showed minimal alterations of red cell morphology. The same morphological defects appeared to be present in the anemic cases as in the patients described by Cooley [*19*]. Although in only one of the Rundles and Falls cases [*20*] had splenectomy been carried out at the time osmotic fragility tests were performed, the tests characteristically showed a wide resistance span with hemolysis beginning at the same salinity as that of the normal control. This, together with their photomicrographs, suggests to us the presence of two fundamentally different red cell populations in the anemic subjects. From other studies [*21*] it is evident that a striking spread in the span of osmotic resistance of erythrocytes develops in individuals subjected to splenectomy. Finally, the authors [*20*] stress that there was a conspicuous absence of skeletal changes in the severely affected subjects, in contrast to the skeletal abnormalities present in thalassemic subjects with comparable anemia.

Dacie [*22*] has briefly referred to a family in London in which several children manifest a severe, refractory, hypochromic anemia, while their mother demonstrates a mild hypochromic anemia. A photomicrograph of a blood smear from an affected male offspring showed erythrocytic defects similar to those encountered in the families already described.

Mills and Lucia [*23*] reported a case of severe hypochromic anemia in a twenty-seven year old man who had splenomegaly and apparently normal osmotic fragility of the red cells. Following splenectomy thrombocythemia and thrombophlebitis of the leg developed; he died six months later with evidence of multiple emboli at autopsy. His half-brother had a similar anemia and thrombophlebitis and died two years following splenectomy.

Mills et al. [*24*] reported a case of a forty-eight year old man with a chronic anemia showing moderate anisocytosis and poikilocytosis of the red cells. He had no splenomegaly, and was unresponsive to a variety of hematinics. The patient was noted to have 30 to 40 per cent siderocytes in his blood smears, an increased plasma iron, normal osmotic fragility of the red cells and a shortened red cell life span. The authors were able to demonstrate decreased red cell iron utilization.

A well studied case of severe hypochromic anemia in a fourteen year old boy was reported by Garby et al. [*25*]. The red cell morphology was strikingly abnormal and included the presence of target cells and microspherocytes with a dominance of hypochromic cells. The red cell osmotic resistance span was increased, the red cell life span was normal, the serum iron was elevated and the iron-binding protein was saturated. There was rapid disappearance of injected isotopic iron from the plasma and diminished utilization of the iron as determined by incorporation into the red cell mass. The patient was treated with pyridoxine and prednisone with no favorable effect on the anemia. A sister was known to be moderately anemic, and on the father's side of the family there were at least two and possibly four other relatives with anemia.

Goldish and Aufderheide [*26*] published an unusual case of hemochromatosis appearing in a fifty-five year old man with long-standing anemia. Although a complete family history was not available, the authors conclude that the anemia most likely belonged to the "hereditary hypochromic" group described by Rundles and Falls [*20*].

On the basis of the marked similarity of hematologic defects in our two cases to those of the patients described, we believe that our patient belongs in the category of "hereditary hypochromic anemia." It may be of some value to refer to this type of anemia as pseudothalassemia.

The persistent and striking erythropoietic response of the marrow in the face of reticulocytopenia and the sporadic occurrence of intense erythroblastemia is somewhat suggestive of a myeloproliferative disorder of the di Guglielmo type. The pouring out of nucleated red cells

into the blood in our patient, however, seemed to coincide with the development of the inflammatory processes. Moreover, our case had no evidence of extra-medullary hematopoiesis.

Harris et al. [*27*] described a severe hypochromic anemia in a thirty-five year old man, presumably associated with abnormalities in tryptophane metabolism, and responsive to parenteral administration of pyridoxine with a striking reticulocytosis and rise in hemoglobin to normal levels. This patient was noted also to have an elevated serum iron, a shortened red cell life span, and increased osmotic resistance of the red cells after twenty-four hours incubation. A recent three-week trial of pyridoxine in our patient showed no significant reticulocyte response or rise of hemoglobin.

Recently a curious type of "hypochromic anemia with hyperferricemia" was described in two patients by Horrigan and his associates [*28*]. In both patients there was an apparent response to a certain liver extract preparation (Valentine's liver extract) in terms of a significant reticulocytosis and a prompt rise in hemoglobin. At present we have been unable to avail ourselves of this particular liver extract; however, a trial of Squibb liver extract produced no significant hematological changes.

The problem of management in our patient has been magnified by the repeated episodes of thrombophlebitis which he has sustained during the past year. At the time of this writing there has been almost total obliteration of the superficial venous system of both legs up to the sapheno-femoral junction. During the course of earlier attacks of phlebitis it was quite evident that no salutary effects were to be derived from the use of anticoagulant measures. At no time, however, has there been evidence of embolic episodes, either with or without the use of anticoagulants. Thrombotic phenomena are known to attend the splenectomized state, possibly due to the thrombocythemia. A variable increase in platelets has occurred in the blood of our patient since splenectomy but this phenomenon has shown no definite relationship to the episodes of thrombophlebitis.

It has been possible to trace roughly the development of a picture of hemachromatosis in our patient. By means of serial biopsies of the liver, the appreciation of a progressive increase in pigmentation of the skin and the performance of glucose tolerance tests, the main diagnostic criteria have been fulfilled. While frank diabetes is not yet apparent, the glucose tolerance curves are characteristic and definite glycosuria has been demonstrated at peak blood sugar concentrations. Within recent years there have been a number of reports of patients with refractory anemias who have manifested some of the features associated with hemochromatosis [*29–36*]. Most of these patients had received a large number of transfusions. In a few cases the estimated or quantitated hemosiderin deposits appeared to be definitely greater than could be accounted for on the basis of total iron from transfusions alone. Our patient has received 26 transfusions to date, or the equivalent of about 6.5 gm. of iron, yet before he had received any blood definite hemosiderin deposits were noted in the liver and portal fibrosis was apparent. It is possible that in this case the capacity for alimentary iron absorption had been altered for some time, due to anemia. It is also possible that the one month of iron therapy prior to hospitalization may have contributed to the deposits of iron.

CONCLUSION

Clinical observations and laboratory data have been accumulated over an eighteen-month period in a patient with an unusual anemia closely resembling a severe thalassemic syndrome. Hematological studies have indicated that the patient's red cells have a shortened life span, which would account in part for the severe anemia. An apparent short-lived beneficial effect from splenectomy was observed, and there appeared to be a slight temporary amelioration of the anemia with prednisone. The patient has presented the additional complications of hemochromatosis, recurrent thrombophlebitis and the occurrence of a localized peritonitis presumably from the perforation of an acutely developing duodenal ulcer. A similar hematological defect has been observed in the patient's brother who has an anemia of less severity. Minor alterations in red cell morphology have been demonstrated in the blood of the patient's sister and mother which are possibly indicative of the inheritance pattern of the anemia under consideration.

It is believed that the anemia herein described resembles the sex-linked or sex-influenced anemia originally described by Cooley [*19*] and later by Rundles and Falls [*20*]. Because of the striking similarity to moderate or severe thalassemia in terms of red blood cell

morphology and evidence of a poorly compensated hemolytic process, it is suggested that the term "pseudothalassemia" be adopted in reference to this type of hemopathic disorder. It is postulated on the basis of the cases published to date that there is in this group of anemias a defect in the synthesis of hemoglobin or in the effective release of erythrocytes from the marrow similar to that defect used [*37*] to explain the essential erythropoietic deficiency in thalassemia.

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Porphyria Cutanea Tarda without Skin Lesion in an American Negro*

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DURING the past several years a great deal of information has become available concerning porphyrin metabolism. The classification of the various porphyrias, however, is still controversial, with the exception of the rare porphyria erythropoietica. Disagreement over classification stems from our lack of precise understanding of the biochemical lesion on the one hand and its relationship to the clinical manifestations of the disease on the other.

"Cutanea tarda" is the name suggested by Waldenström for the type of porphyria which is characterized by the appearance of skin lesions late in life, partly due to photosensitivity. This clinical syndrome is usually associated with hepatocellular injury. Typically there are large amounts of preformed porphyrins in the liver which are probably excreted via the bile into the intestine and account for the characteristically large amounts of fecal porphyrins. Varying amounts of uroporphyrins are present in the urine and the urinary coproporphyrin also is usually elevated. As a rule, porphobilinogen is absent from the urine. If there is an etiologic relationship between the abnormal porphyrin metabolism and the hepatic lesions in porphyria cutanea tarda it is not yet established, nor is it clear whether or not both are an effect of a common, yet unidentified cause.

Porphyria cutanea tarda has not yet been described in the American Negro. This case is reported to point out that the metabolic derangement characteristic of porphyria cutanea tarda can occur in the American Negro without skin lesions of any sort, and to call attention to a possible etiologic role which this underlying metabolic error may play in the development of hepatocellular injury.

METHOD

Urinary coproporphyrin (UCP) was determined as described by Schwartz et al. [*1*]; urinary uroporphyrin (UUP) and the fraction soluble in ethyl acetate at pH 3.1 (the so-called "type 3" uroporphyrin) were measured as described by Sveinsson et al. [*2*] and by With [*3*]. The erythrocyte porphyrins were determined as described by Schwartz and Wicoff [*1*]. This method was adapted also to measurement of the ethyl acetate-acetic acid soluble fecal porphyrins. The fraction extractable by 0.1 N HCl and insoluble in chloroform is called fecal coproporphyrin (FCP) and the fraction extracted by 3 N HCl is called fecal protoporphyrin (FPP). The total ethyl acetate-acetic acid insoluble fecal porphyrin was measured in the following manner: after the ethyl acetate-acetic acid failed to remove any more colored or fluorescent material, the fecal residue was extracted with 1.5 N HCl. The porphyrin concentration in this clear hydrochloric acid extract was measured fluorometrically against a coproporphyrin standard. The hydrochloric acid was neutralized to congo red paper by the addition of saturated solution of sodium acetate, and the uroporphyrin concentration was determined by the method of Schwartz et al. [*5*].

Urinary urobilinogen and porphobilinogen were determined by the method of Watson and Schwartz [*6*] and urobilin was detected by the Schlesinger [*7*] test.

CASE REPORT

A. S. (No. 323470), a Negro male farm laborer, was in excellent health during the first fifty-three years of his life. The first abnormality he noted was a red discoloration of his urine which appeared on a number of occasions in 1948. At about the same time he had recurrent episodes of swelling and pain in his right knee. There was an apparent association between this "red urine" and the arthritis. These episodes lasted a few days at a time, with remissions of four to five weeks between recurrences. In April 1949,

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he was hospitalized at Grady Memorial Hospital because of acute pyogenic arthritis of the left knee and septicemia. The patient consumed a good diet and drank alcohol only in moderation. There was no evidence of any skin lesion, hypertrichosis, abnormal pigmentation, neuropathy, abdominal pain or hypertension. The liver and spleen were not enlarged. Examination of the genitourinary tract revealed only chronic prostatitis. Laboratory findings demonstrated no anemia; the leukocytosis paralleled his clinical course. E. coli was cultured from the joint fluid and blood. The total serum protein was 6.4 gm. and again 6.0 gm. per 100 ml. The formol gel test was negative. The icterus index varied between 11 and 25 units. The cephalin flocculation test varied between negative to 2 plus, and the thymol turbidity was 0 and 2 units on repeated examinations. The total serum bilirubin was 0.6 mg. per 100 ml. Bromsulphalein retention after the administration of 5 mg. per kg. was 24 per cent in thirty minutes and 12 per cent in forty-five minutes. The prothrombin time was normal repeatedly. The gallbladder did not visualize after ingestion of priodox. The urine was dark red during the first twenty-four days of his hospitalization. On repeated examinations only urobilinogen but no porphobilinogen was found. The urine contained no protein and no erythrocytes. The patient responded to antimicrobial therapy, made a good recovery, and was discharged after six weeks of hospitalization.

He returned to his farm work and had no complaints for six years. In the summer of 1955, at the age of fifty-nine years, he noted progressively increasing exertional dyspnea. In July, 1955, he noted that his urine became dark red and an "influenza-like" illness developed with chills, fever, dyspnea, myalgia, malaise, weakness, cramping abdominal pains and rather severe diarrhea. He was again hospitalized from August 1, 1955, to September 22, 1955. Examination demonstrated no skin lesions. He was hypertensive, the blood pressure being 150/100 mm. Hg, which decreased to 124/84 mm. Hg during his hospital stay. He had cardiomegaly and auricular fibrillation alternating with normal sinus rhythm. There was evidence of pulmonary infarctions and congestive heart failure.

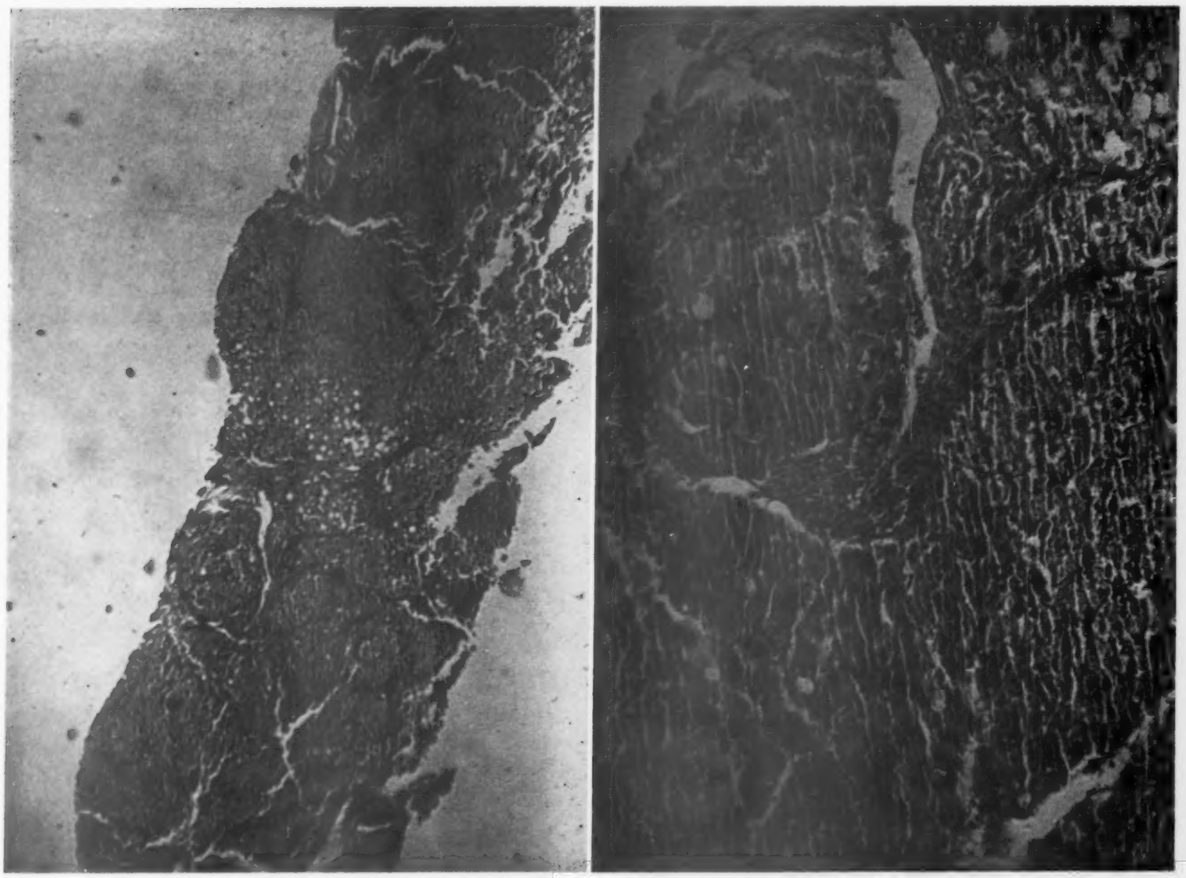
The laboratory findings demonstrated no anemia or leukocytosis. The blood urea nitrogen was 15 mg. per cent. The total serum protein was 6.2 and 6.8 gm. per 100 ml. with albumin 2.1 and 2.4 gm. per 100 ml., respectively. Serum electrophoresis showed "greatly elevated gamma globulin." The cephalin flocculation test was 4 plus repeatedly. The thymol turbidity test ranged from 9½ to 16 units. The total serum bilirubin was 2.7 mg. per 100 ml. on admission and fell to 1.0 mg. per 100 ml. in two weeks; the direct fraction was 1.6 mg. per 100 ml. on admission and fell to 0.4 mg. in two weeks and to 0.2 mg. per 100 ml. in seven weeks. Bromsulphalein retention at forty-five minutes was consistently over 40 per cent. The prothrombin time was 15.6 seconds with the control of 14.6 seconds. The serum alkaline phosphatase was 2.7 Bodansky units. Bacteriologic studies of sputum, blood, urine and stool revealed no pathogens. His urine was dark brownish red for six weeks. Numerous examinations of fresh urine specimens were negative for porphobilinogen but very strongly positive for urobilinogen and urobilin.

Urinary porphyrin analysis revealed the excretion of large amounts of urinary coproporphyrins. The urinary uroporphyrin excretion was 2.5 mg. per twenty-four hours. The patient responded well to therapy designed to treat his congestive heart failure. A needle biopsy of the liver was performed (Fig. 1) and revealed a moderate portal fibrosis with portal infiltrates and translobular septation showing early pseudolobulation not sufficient to justify the diagnosis of cirrhosis. Rather large amounts of hemosiderin were seen in the liver cells and Kupffer cells. Examination with the ultraviolet microscope clearly showed a marked excess of free porphyrins.

Following his discharge from the hospital the patient felt well and had only mild exertional dyspnea in spite of the fact that he discontinued taking digitalis. However, he did not feel strong enough to return to work. He was seen in the outpatient clinic in March, 1956. No unusual findings were discovered on examination. Laboratory results showed a total serum bilirubin of 0.36 mg. per 100 ml., direct 0.16 mg. per 100 ml. Bromsulphalein retention of 32 per cent in forty-five minutes. zinc sulfate turbidity 12.8 units, cephalin flocculation test was negative, thymol turbidity 9.5 units. The urine was yellow in color; it was negative for porphobilinogen. Urinary coproporphyrin excretion was 0.797 mg. per twenty-four hours; the UUP was 4.449 mg. per twenty-four hours, 87 per cent of this was the "type 3" variety.

In April, 1956, he had a cerebrovascular accident which produced a permanent hemiplegia on the left side. In March, 1957, he was seen at his home. He felt well although he noted occasional mild abdominal discomfort relieved by defecation. Examination revealed the left hemiplegia but no other abnormal findings. Repeated examinations of fresh urine were negative for porphobilinogen.

On March 2, 1957, the twenty-four-hour UCP excretion was 0.70 mg. The twenty-four-hour UUP was 3.51 mg., of which 78 per cent was the "type 3" variety. The fecal coproporphyrin was 6.58 mg. per 100 gm. and the fecal protoporphyrin was 4.92 mg. per 100 gm. On March 7, the twenty-four-hour UCP excretion was 0.65 mg. and the UUP was 4.4 mg. of which 75 per cent was "type 3." The fecal coproporphyrin was 5.71 mg. per 100 gm., the fecal protoporphyrin was 2.98 mg. per 100 gm. and ethyl acetate-acetic acid insoluble but 1.5 N HCL soluble porphyrin was 5.2 mg. per 100 gm. as measured directly against a coproporphyrin standard. Fecal uroporphyrin was 1.0 mg. per 100 gm. Between April 24, and May 2, fourteen consecutive twelve-



1A 1B

FIG. 1. Moderate portal fibrosis is seen with portal infiltrates and translobular septation. There is early pseudolobulation but no cirrhosis. A, original magnification × 100. B, original magnification × 600.

hour urines were collected to evaluate the day and night as well as the day-to-day variation of UCP and UUP. (Table I.)

On April 24 the hemoglobin was 14.2 gm. per 100 ml. and the reticulocyte percentage was 1.6. The erythrocyte coproporphyrin was 8.0 μg. per 100 ml. red blood cells and the erythrocyte protoporphyrin was 24.2 μg. per 100 ml. red blood cells. The plasma did not show the magenta fluorescence of porphyrins when exposed to near ultraviolet light.

COMMENTS

It is difficult to fit this patient into any of the existing classifications of the porphyrias. The absence of photosensitivity and the lack of cutaneous lesions due to the deranged porphyrin metabolism in this elderly man make it rather awkward to classify this case as cutaneous porphyria. On the other hand, the presence of preformed porphyrins in the liver, the fecal excretion of increased quantities of porphyrins and the urinary excretion of large amounts of uro type prophyrins are characteristic of porphyria cutanea tarda (PCT) [*9*].

There is no clear-cut explanation for the absence of photosensitivity in this patient. The pigment content and the hornified layer of the skin in the Negroes in America may provide adequate protection against the photosensitizing effect of the near ultraviolet spectrum of solar radiation. Observations of cattle with porphyria [*8*] and sheep with photosensitivity [*10*] would support this hypothesis. However, the rather common occurrence of PCT with skin lesions among the Bantus in South Africa [*11,12*] demonstrates that photosensitivity can occur in Negroes. Of course, the greater intensity of solar ultraviolet radiation in South Africa may be an acceptable explanation [*12*] but Koller [*13*] believes that there is only a small difference in the intensity of ultraviolet between tropical and temperate latitudes. Another explanation for the lack of skin lesions in this pa-

TABLE 1
EXCRETION OF URINARY PORPHYRINS

No.	Time	UCP (μg./12 hr.)	UUP (μg./12 hr.)	"Type 3" UUP (%)	No.	UCP* (μg./24 hr.)	UUP* (μg./24 hr.)
1a	Night	138.1	2240.0	..			
1b	Day	275.6	1508.0	..	1	413.7	3748.0
2a	Night	216.0	2160.0	65			
2b	Day	180.0	1600.0	75	2	396.0	3760.0
3a	Night	154.7	1905.0	75			
3b	Day	206.4	1419.0	69	3	361.1	3324.0
4a	Night	106.2	1075.0	76			
4b	Day	226.8	1974.0	..	4	323.0	3049.0
5a	Night	158.4	1650.0	..			
5b	Day	279.0	1674.0	..	5	437.4	3324.0
6a	Night	230.3	2115.0	..			
6b	Day	254.2	1517.0	73	6	484.5	3632.0
7a	Night	133.7	1428.0	..			
7b	Day	246.4	2279.0	..	7	380.1	2707.0

* Calculated.

tient is that an adequate amount of porphyrin in a form capable of producing photosensitivity did not penetrate the cells of the epidermis.

The location of the metabolic error in the chain of events in the porphyrin metabolic cycle may be a determining factor in the development of photosensitivity. The urinary excretion of delta-aminolevulinic acid and of porphobilinogen in acute porphyria is usually associated with abdominal and neurological symptoms. In pure cutaneous porphyria, however, these compounds are usually absent and the disease is associated with the excretion of increased quantities of free porphyrins in the stool and urine and with large amounts of preformed porphyrins in the liver. It is quite possible that the so-called cutaneous porphyria is not a homogeneous group. The location of the predominant biochemical lesion and the resulting metabolic abnormality may determine the clinical manifestations of the disease.

Gray et al. [*14*] and MacGregor et al. [*15*] have reported two similar and well studied cases of PCT with episodes of marked photosensitivity. In their patients acute exacerbations of the disease were precipitated by jaundice associated with hepatocellular injury and consequently by the "diversion" of the fecal porphyrins via the plasma to the urine. Neither of these patients had had more than a trace of ether-insoluble fecal porphyrins. Large amounts of ether-insoluble porphyrins were found in the serum of these patients during exacerbation of their disease, suggesting a more fundamental metabolic defect than simple diversion. In the present patient there was a large amount of uro type porphyrin in the feces. He did not exhibit sensitivity to light, in spite of known exposure to midsummer sun, even during an episode of jaundice with pronounced impairment of hepatocellular function. One explanation could be that the metabolic error in the porphyrin anabolic system involved different reactions in this patient than in the ones reported by Gray et al. and MacGregor et al.

A questionable instance of photosensitivity was reported in an American Negro with porphyria in a recent communication. Smith and Frumin [*16*] reported a case of "paroxysmal nocturnal porphyrinuria" in a forty-three year old Negro whose urine became red when he was kept in a recumbent position. He gave a history of increased skin pigmentation in exposed areas. He also had urticaria and angioneurotic edema probably due to drug hypersensitivity. He excreted large amounts of UUP but no porphobilinogen. Unfortunately, from the data presented it is not clear whether this patient excreted porphyrins only at night, as the authors suggested, or also during the day. The findings could be compatible with porphyria cutanea tarda but the evidence is inconclusive.

There is a striking relationship between PCT and parenchymal liver disease. The sequence

of events in the patient presented in this communication suggests a possible etiologic relationship between the impaired porphyrin metabolism and the subsequent liver disease.

The two hospital admissions of this patient was accompanied by prolonged excretion of dark

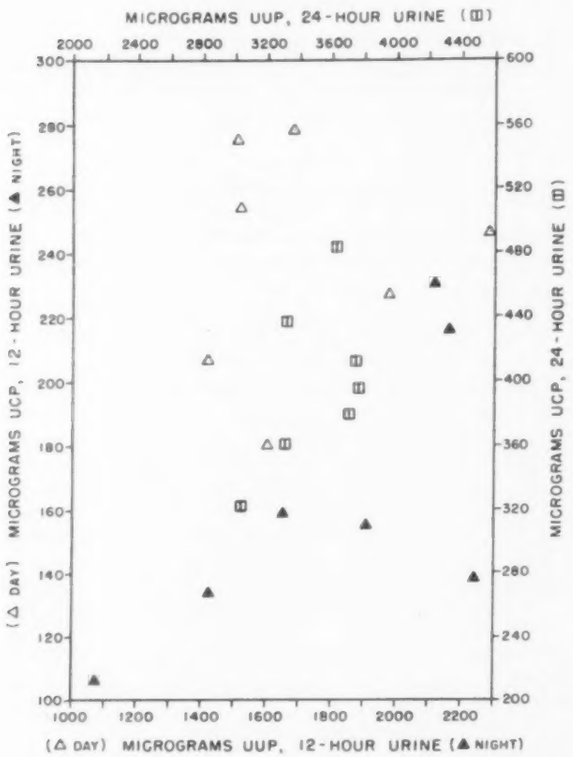


FIG. 2. Scattergram describing the variations in UUP and UCP relationship in fourteen consecutive twelve-hour urine samples (measured) and in seven consecutive twenty-four-hour urine samples (calculated).

red-brown urine. This was associated with jaundice during the second hospitalization. Unfortunately, no porphyrin analyses were made on the urine during the first admission and on the feces during the first and second hospital admissions. However, the strikingly similar appearance of the urine on these two occasions would suggest that the biochemical abnormality of the urine during these two periods was probably the same. It is difficult to account for this abnormal urinary finding on the first admission on the basis of an unrelated disturbance of pigment metabolism. The intermittent excretion of red colored urine during recurrent attacks of arthritis in 1948 and 1949, and the prolonged excretion of dark red-blown urine during an episode of pyogenic arthritis and bacteremia in 1949 may be related. During his first hospitalization there was no convincing evidence of liver disease. The slightly elevated retention of bromsulphalein was observed while the patient was still acutely ill and febrile, and it returned to normal during convalescence.

There is a well established association of abnormal porphyrin excretion and bacterial infections, and arthritis [*17*]. It seems quite probable that those factors which alter normal porphyrin metabolism also may influence it in a person with latent porphyria. The magnitude and the direction of these effects, of course, could be quite different in the latter. In the present case some of the yet unidentified factors associated with an acute febrile disease made a latent metabolic defect symptomatic at a time when significant liver disease was not yet demonstrable.

During the subsequent seven years some kind of liver disease developed. This was manifested by the persistent abnormality of the so-called liver function tests and by the morphologic findings in the liver biopsy specimen. It is suggested that this sequence of events represents a defect or deficiency in the liver cell involving one or more stages of the porphyrin metabolic system. During increased demand on this system the metabolic fault became clinically manifest. When this metabolic imbalance can no longer be compensated adequately, cellular injury occurs which results in functional as well as morphologic changes in the liver. This sequence of events may be in a sense analogous to the observations of Best et al. [*18*] and Klatskin [*19*] who noted in the experimental animal that sucrose and alcohol increase the choline requirement and that the diet must be at least marginal in its lipotropic factor content before the injurious effect of alcohol becomes evident. This is a clear demonstration of the fact that a suboptimal but compensated metabolic process in the liver cell may not result in cellular injury as long as the metabolic demand does not exceed the capacity of the system. However, if the metabolic demand increases beyond a critical point cellular injury may occur. Further hepatocellular injury by any other agent in such patients may well produce exacerbation of a pre-existing metabolic defect and could precipitate attacks of cutaneous porphyria [*8,14,15*].

The relationship between the excretion of UUP and UCP is illustrated in Figure 2. Casual observation of the relationship between the

twenty-four hour excretions of UUP and UCP would suggest a fairly consistent relationship since the scattergram approximates a straight line. The correlation coefficient r = 0.33, however, shows that this observed relationship could have occurred by chance in 40 per cent to 50 per cent of the cases. The lack of a good correlation is evident as one observes the relationship of the twelve-hour day and night urines. The correlation coefficient is r = 0.07 for the day urines; and for the night urines r = 0.65. This means that there is almost no relationship between the UCP and UUP excretions during the day as r approaches 0.0, and for the night urines the observed relationship could have occurred by chance alone 10 per cent to 20 per cent of the time. There is a very striking difference of the UUP/UCP relationship between the day and night urines, as the scattergrams of these two groups are distinctly separable by a straight line. These observations are incompatible with any theory suggesting a common mechanism for excretion of the large amounts of UUP and and for the increased amounts of UCP. Further studies are required to determine whether this observed difference in the diurnal excretion patterns of UCP and UUP is due to separate mechanisms or additional factors affecting the excretion of one and not the other porphyrin.

SUMMARY

Porphyria cutanea tarda (PCT) without skin lesions is described in an American Negro. Large amounts of free porphyrins were present in the liver of this patient; he excreted greatly increased quantities of fecal porphyrins; the urine contained large quantities of uroporphyrins, and increased amounts of coproporphyrins. No porphobilinogen was detectable on numerous examinations.

The possible reasons for the absence of photosensitivity in this patient are discussed.

There was no evidence of parenchymal liver disease until seven years after the first signs of porphyria. It is suggested that the underlying biochemical lesion caused not only the abnormality in the porphyrin metabolism but also could have been responsible for the subsequent development of hepatocellular injury.

There was no demonstrable correlation in the diurnal excretion patterns of urinary coproporphyrin (UCP) and urinary uroporphyrin (UUP).

Acknowledgment: I wish to express my gratitude to Dr. Leo Krainer, Armed Forces Institute of Pathology and to Dr. Cecil T. Watson, Professor of Medicine, University of Minnesota, for reviewing the liver biopsy specimen and for examining it with the ultraviolet microscope.

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Right Atrial Myxoma*

A Clinical Study of a Patient in Whom Diagnosis Was Made by Angiocardiography during Life. (Surgically Removed)

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THE recent advances in the surgical treatment of cardiac abnormalities make it imperative for an antemortem diagnosis of an intracavitary tumor to be made. The clinical diagnosis of this type abnormality is a rarity. Mahaim suggested that angiocardiography might afford a means for the identification of cardiac tumors during life [*1*], and it has since been shown to provide an effective method for diagnosis. Three patients with left atrial myxomas have been correctly diagnosed during life by Steinberg and his associates [*2*].

Prichard [*3*] and Mahaim [*1*] have presented the best reviews on this subject. The former author has fully discussed myxoma and points out that rarely is it diagnosed during life. His review states that 75 per cent of atrial myxomas are left-sided and 25 per cent occur in the right atrium. Clinically, the localization of the tumor is important. A determination of its size will also be necessary for the determination of the urgency of operation. Since intracavitary tumors originate almost exclusively in the atria, and these tumors produce obstruction of the outflow from the atria, the most characteristic clinical picture is that of stenosis, occasionally regurgitation, or a combination of both; when in the left atria, mitral stenosis, and when in the right, stenosis of the tricuspid valve.

The following is the case report of a patient who appeared to have clinical tricuspid stenosis and who was demonstrated by angiocardiography to have a non-opacified mass in the right atrium diagnosed as an atrial myxoma and proved so at operation.

CASE HISTORY

A fifty-one year old man had progressive right-sided heart failure for five months. Two weeks before being seen, the patient had been having syncopal attacks. The past history was free of rheumatic infection or any cardiac disease. Distended neck veins and a loud presystolic murmur which was heard loudest in the tricuspid area were found. This murmur was markedly intensified by deep inspiration and became almost inaudible when the breath was held. A phonocardiographic study recorded this phenomenon, and showed that there was also a late diastolic murmur; the intensity of both these murmurs was greatly altered by the respiratory phase. (Fig. 1.) The chest roentgenogram showed an enlarged cardiac shadow with a fullness and straightening of the left border. There was a suggestive double shadow at the right border. The lungs were strikingly free of vascular engorgement. (Fig. 2.)

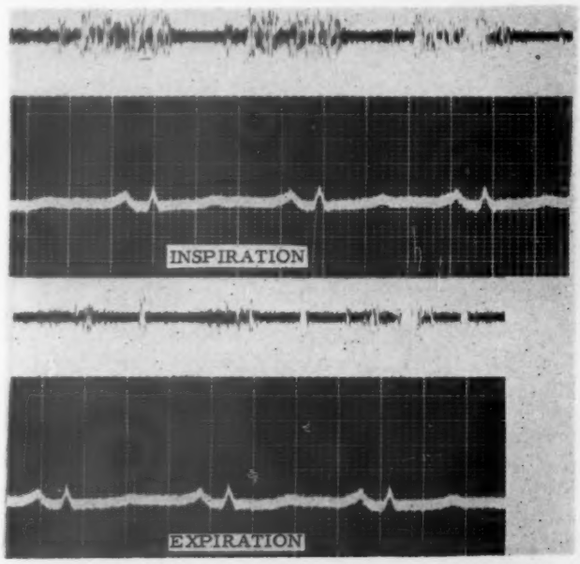

FIG. 1. The phonocardiographic record of the patient demonstrating the influence of respiration on the presystolic murmur.

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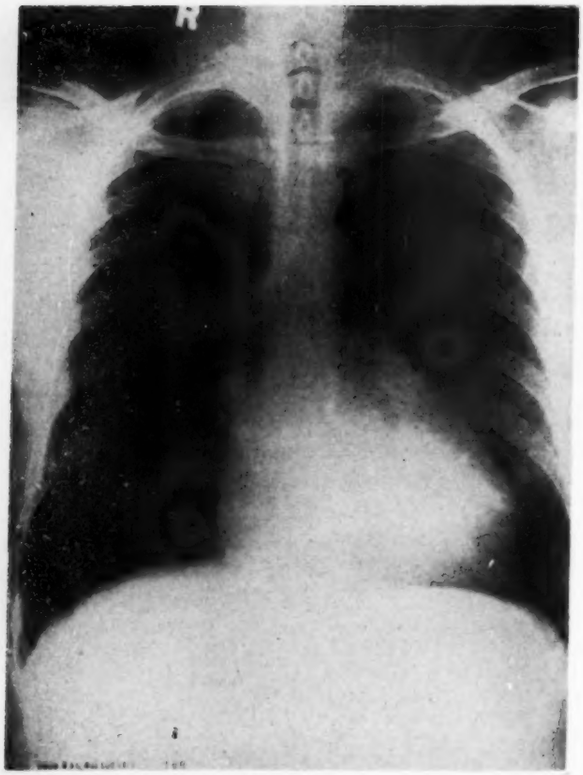

FIG. 2. The posteroanterior chest roentgenogram, which shows a large heart with fairly clear lung fields.

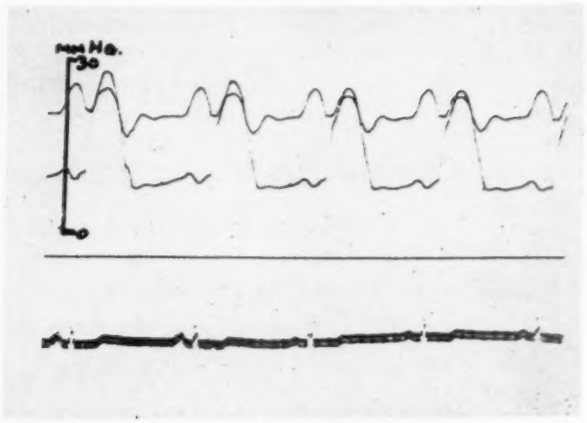

FIG. 3. The cardiac catheterization record of simultaneous auricular and ventricular pressure curves showing the gradient between auricle and ventricle.

Urinary tests for 5 hydroxyindolacetic acid (serotonin derivatives) were negative. The electrocardiogram showed normal sinus rhythm, a rate of 85 per minute, PR interval 0.16 seconds, QRS interval 0.07 seconds, QT interval 0.36 seconds. A tendency to right axis deviation was present. There were giant P waves in leads II, III and V. A QS pattern was present in V_1 and V_2. This study was interpreted as showing right auricular hypertrophy. A tracing of the jugular pulse showed a large giant A wave, and a small delayed V wave.

Cardiac catheterization was performed and the mean pressure gradient between the right auricle and right ventricle was 26 mm. Hg. The auricular pressure curve was characteristic of tricuspid stenosis. (Fig. 3.)

An angiocardiographic study was made and a large non-opacified mass was noted in the right auricle in both posteroanterior and right lateral views. (Figs. 4A, 4B, 5A and 5B.) This measured 9 cm. by 11 cm. The superior vena cava was dilated; the right ventricle was never well opacified.

An operation was performed by Dr. Clarence Dennis. The patient's chest was explored through a transverse incision, dividing the sternum. After the pericardium was opened, there was found a huge right atrium, palpation of which revealed it to be virtually filled with a firm mass. The ventricles appeared flabby and heavily infiltrated with fat. Following heparinization, a plastic catheter for return of oxygenated blood from the pump-oxygenator machine was placed in the aorta through the left subclavian artery. Plastic catheters for withdrawal of blood for cardiac by-pass were, with some difficulty, threaded from the atrial appendage past the tumor mass and into the two cavae. With perfusion started at 1,800 cc. per minute, the cavae were occluded at the junctions with the atrium by means of preplaced ties, and the right atrium was widely opened. The ventricles were electrically fibrillated to avoid air embolism. Examination within the heart showed a huge tumor which filled the right atrium and appeared to pass downward somewhat into the inferior vena cava and into the right ventricle to a considerable degree. The tumor from cephalad to caudad dimension was 9 cm. Transversely, it was 8.5 cm. and the anteroposterior dimension was 5.5 cm. It was barely possible to pass the finger from the left side of the patient through the atrioventricular ring and to deliver the tumor into the large incision which had been made in the atrial wall. Following this, the tumor was cautiously dissected from attachments in the septum and removed. Following removal, the atrial septum was examined and the site of attachment to the tumor adjacent to the coronary sinus was noted. The area of attachment extended superiorly to the foramen ovale and extended somewhat anteriorly across the septum as well. The area of attachment was approximately 3 cm. in diameter. At this point it was observed that all four fingers of one hand could be passed into the right ventricle through the AV ring as if the ring proper did not exist at all. This did not cause concern at the moment because of the knowledge that the pressure of 25 cm. of blood in the right atrium observed preoperatively is high enough for perfusion of the pulmonary arterial tree. Therefore, no effort was made to deal with the huge tricuspid insufficiency which had been created by removal of the tumor. Following closure of the atrium, the heart was readily

FIG. 4A. The posteroanterior angiocardiogram showing the right auricular area of non-opacification.

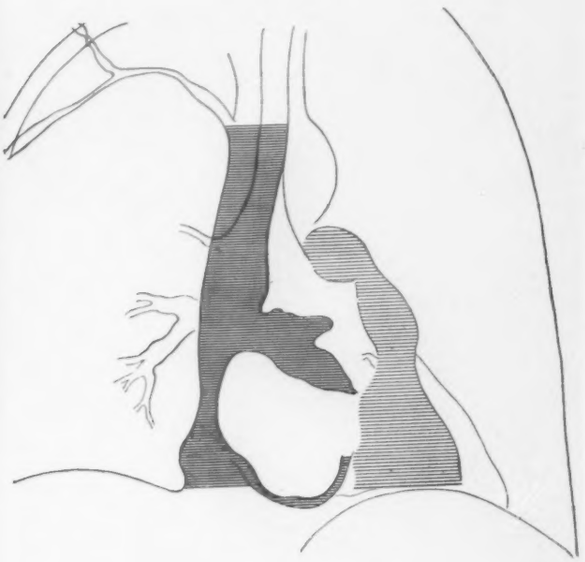

FIG. 4B. The diagram of the angiocardiographic finding.

defibrillated with a single shock. Following evaluation of the patient's general status and while the heart-lung machine was delivering about 2½ L. per minute, it was observed that the patient had occasional respiratory movements, that the pupils were moderately small, and that there was a good corneal reflex. The attachments to the heart-lung machine were therefore removed. Atrioventricular dissociation supervened almost at once, but the patient maintained a reasonable blood pressure, and closure of the chest was performed. A normal sinus rhythm with a rate of 90 to 95 per minute returned only to convert suddenly to an ectopic ventricular rhythm for three or four beats, and then frank ventricular fibrillation. The chest was opened rapidly and the heart was defibrillated with apparent success but again failed and fibrillated, and all efforts to revive the heart failed.

The mechanism of failure was suspected to rest in a very flabby myocardium upon which was superimposed an abrupt conversion of a high grade tricuspid stenosis to a total tricuspid insufficiency, and the trauma of the operative intervention.

The large myxomatous glistening tumor had an indentation at its inferior margin from the impression of the valves where it obstructed the tricuspid orifice. (Figs. 6 and 7.) There were also small nodules of tumors on the tricuspid valve surface. The histologic examination showed the typical acellular, myxomatous tissue with the plasma cells of a fibromyxoma.

CLINICAL FINDINGS

Since the growing tumor interferes with valvular function or mechanically obstructs the orifice of the valves, exertional dyspnea is a common finding, as in this patient. Cardiac failure, when it develops, usually does not respond well to the usual measures because it is due to mechanical interference with atrial or ventricular filling, or both. Because of this factor cardiac output is markedly reduced. In right-sided obstruction the absence of congestion in the pulmonary fields is a valuable sign. In the left-sided atrial myxomas, angina may be a prominent symptom resulting from the marked pulmonary hypertension, the reduced cardiac output and subsequent reduced coronary artery flow. Embolic phenomena may be a striking finding. These arise from fragmentation of the tumor, or more probably from dislodgement of surface thrombi. Establishment of the definite absence of murmurs until the onset of the illness is an important fact for the consideration of a intracavitary tumor. Syncope, especially when it

FIG. 5A. The right lateral angiocardiographic study showing the large area of non-opacification in the right auricle.

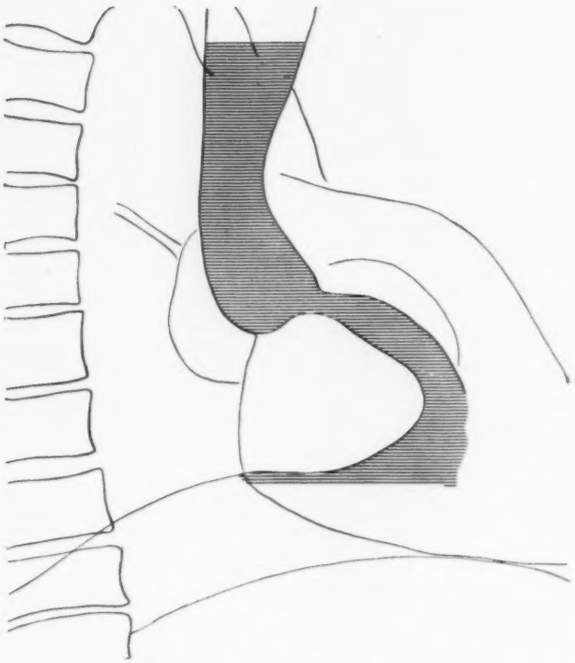

FIG. 5B. The diagram of the angiocardiographic finding in this view.

occurs with change of body position, is an excellent clue to the presence of a tumor in the heart chamber. Arrhythmias are not uncommon. Unexplained episodes of dyspnea, cyanosis and orthopnea are also valuable signs. Occurrence of these symptoms and signs with change of position of the patient certainly will make the diagnosis more likely. Other features in association with positional changes, such as variation in symptoms and changes in auscultatory and other physical signs, are most helpful for establishing this diagnosis.

CARDIAC CATHETERIZATION FINDINGS

In this patient a pressure gradient of 26 mm. Hg was found from the right atrium to the right ventricle. The atrial pressure was abnormally elevated. Cardiac output was reduced and there was obstruction to the outflow from the atrium. The data obtained in the study of the patients with left atrial myxoma was similar to that found in patients with valvular obstruction (mitral stenosis). There have been seven other patients with myxomas who had undergone cardiac catheterization. Of these patients only one had a right atrial myxoma [*4*].

It is uncertain whether or not cardiac catheterization can ever show more than interference with atrial emptying. This was the situation in our patient. However, Bayer and his associates [*5*] interpreted their cardiac catheterization data as suggestive of a mass at the tricuspid valve. Their case, however, was not a proved myxoma; yet the angiocardiographic study tended to confirm this impression.

ANGIOCARDIOGRAPHY

Angiocardiography is the definitive diagnostic method for establishing the diagnosis of an intracavitary tumor. The characteristic filling defect is noted in every reported case [*2,4–7*]. Atrial thrombi produce filling defects which are usually not homogenous, and show irregular opacification in the atrial chamber [*8*]. In addition, atrial myxoma may prolapse through the orifice of the valve and produce a filling defect in the ventricular cavity; this would be an unusual characteristic for atrial thrombi. However, a ball-valve thrombus of considerable size might

FIG. 6. The tumor after removal showing its glistening surface and the indentation where the valves seated.

FIG. 7. The lateral surface and appearance of the tumor.

offer considerable difficulty. A case of this type of atrial thrombus has been reported [*8*]. The angiocardiographic measurements of the tumor can give information about the size to be expected at surgery. The attachment by a pedicle or a sessile attachment may be predicted by study of the angiocardiographic films. In spite of the frequency of a pedicle attachment, the angiocardiographic study in our patient indicated a sessile attachment which was confirmed at the time of operation.

Emphasis must be placed upon the fact that angiocardiography is necessary and the only definite means for the diagnosis of an intracavitary cardiac tumor during life.

The cardiac intracavitary tumors are of two types: myxoma and sarcoma. The myxoma is the most common and comprises 50 per cent of all primary cardiac tumors [*3*]. There is an equal sex distribution. The earliest age in which a myxoma was reported was three months, the latest, sixty-eight years. The majority occur in the age group between thirty and sixty years. The myxoma generally arises from the atrial septum by a small pedicle in the region of the fossa ovalis. Seventy-five per cent of these tumors are found in the left atrium and the remaining in the right atrium. An extra-atrial location does occur but is extremely rare. Atrial myxomas may be small and cause no symptoms; they are found as an incidental autopsy finding. The previous arguments of these not being neoplasms are no longer held. In fact, Ringertz [*11*] reported the growth of embolic fragments of a myxoma in the mesenteric arteries and the brain. It is considered a benign neoplasm, since there is never any hematogenous spread, local invasion or cytologic characteristics of malignancy, but embolic fragments may give it the significance of malignancy. This latter occurrence must be extremely rare. In one such case, a diagnosis was established after a myxomatous embolus was removed from the leg of a patient.

The pathologic studies show that the myxomas are generally smooth, most commonly pedunculated. They are yellowish or whitish in color, and may have areas of hemorrhage. There may be thrombi formation on the surface. Microscopic study usually shows an endocardial lining. The tissue is almost acellular. Multinuclear, stellate cells and focal collections of plasma cells and lymphocytes are found. Bone, calcium and

collagen deposits may be present. Cystic spaces may be found in the body of the mass.

Sarcomas are predominantly mural tumors. They may give symptoms similar to those of the myxomas. They occur within the same age group and have the same sex distribution. The most marked difference is the equal involvement of atria and ventricles. The clinical symptoms, similar to those of myxoma, are frequently associated with hemopericardium, arrhythmias, and more marked inferior and superior vena caval obstruction. There is a rapid progression of the clinical course because this type of tumor grows rapidly. These clinical symptom associations are not those of myxoma.

SURGICAL TREATMENT

Every effort should be made to establish the diagnosis of an atrial intracavitary tumor. The differentiation between a thrombus or a myxoma is academic. Recently, reports of mass thrombus of the right atrium have appeared. Occlusion of the tricuspid valve with clinical signs and physiologic disturbances similar to those of myxoma have been noted [*9,10*]. Since angiocardiography is the only definitive diagnostic method, it should be employed in every patient suspected of having this disease.

With the advent of the recent advances in cardiac surgery it is possible that removals will be accomplished successfully more frequently. Bahnson and Newman [*4*], and Davis and Bedford [*12*] have removed successfully, a myxoma from the left atrium. Others have also been able to do this [*7,14–16*]. A recent report of the successful removal of a teratoma of the atrium has appeared. Artificial heart-lung apparatuses, hypothermia, improved physiologic knowledge, all foretell of an optimum method for the treatment of intracavitary cardiac tumors [*13–19*].

SUMMARY

A patient with a right atrial myxoma in whom diagnosis was made during life is discussed. The presence of a valvular stenosis, in this case tricuspid stenosis, and the history of sudden onset with progression and syncopal attacks are suggestive of an intracavitary cardiac tumor. Angiocardiography is essential for the diagnosis *in vivo*.

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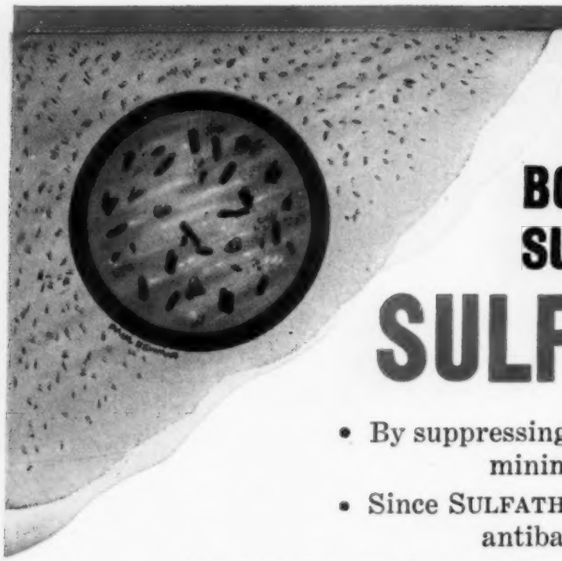

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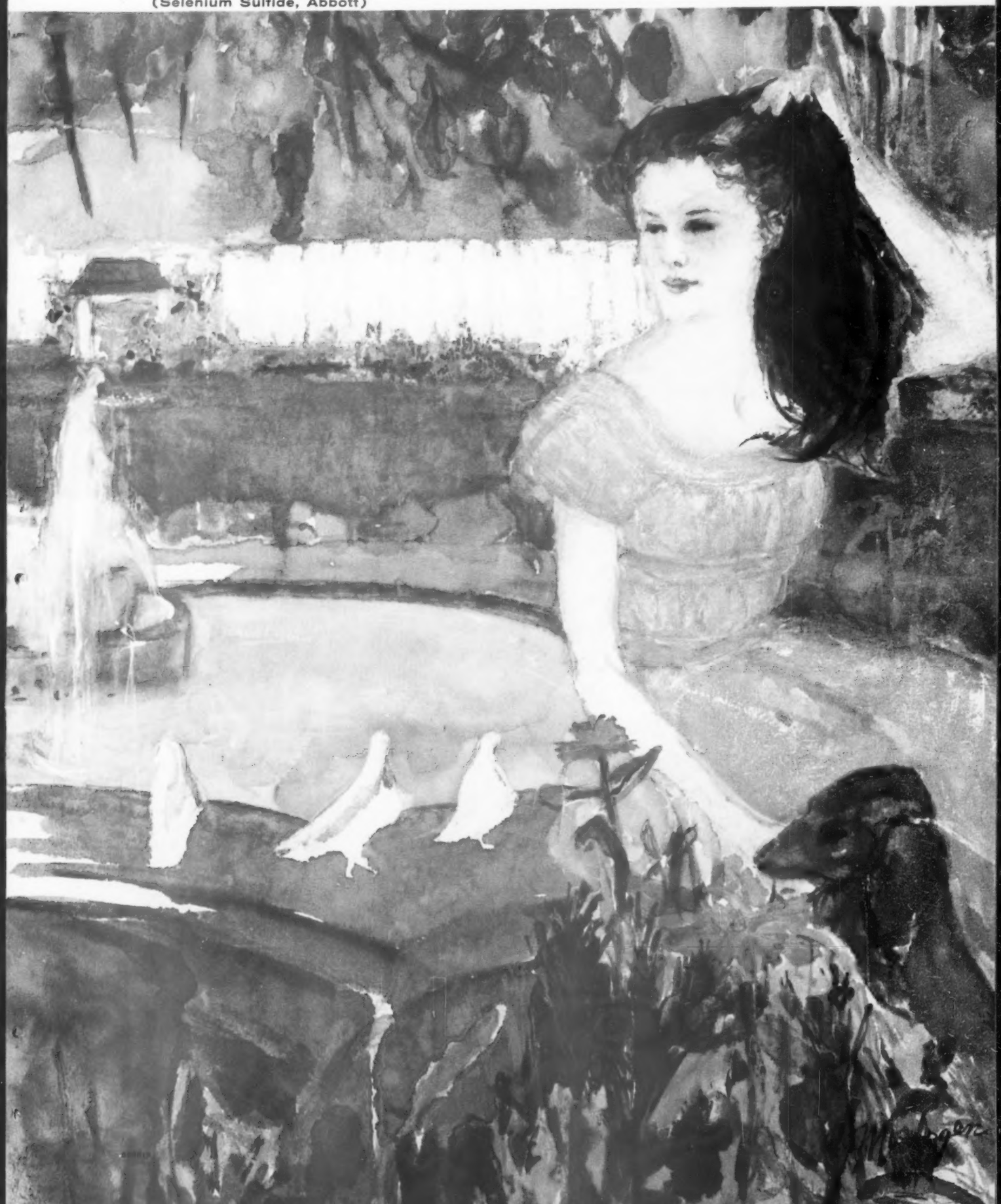

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References: *1. Goodman, D. H.: Arizona Med. 13:389, 1956. 2. Nicholson, J. H., and Leavitt, T., Jr.: New England J. Med. 255:491, 1956. 3. Nicholson, J. H.: Angiology 8:456, 1957. 4. Pollock, B. E.: J.A.M.A. 159:1094, 1955; 161:404, 1956. 5. Shapiro, S.: Surg. Clin. North America, Apr., 1956. 6. Kerrin, H. F., et al.: Angiology 8:308, 1957. 7. Brotman, I.: Am. J. Cardiol. 1:260, 1958. 8. Fremont, R. E., and Jagendorf, B.: J.A.M.A. 165:1381, 1957. 9. Link, K. P.: Paper presented at New York Acad. Med., Feb. 25, 1958, New York, N. Y. 10. Council on Pharmacy and Chemistry, A.M.A.: J.A.M.A. 159:1297, 1955. 11. Shapiro, S.: Angiology 6:498, 1955. 12. Olwin, J. H., and Koppel, J. L.: A.M.A. Arch. Int. Med. 100:848, 1957. 13. Clatanoff, D. V., and Meyer, O. O.: Ibid. 97:753, 1956. 14. Shapiro, S., and Ciferri, F. E.: J.A.M.A. 165:1377, 1957.*

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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

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Source—Meyer, O. O.: Northwest Med. *53*:1006, 1954.

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*Bauer, H. G.; Seegers, W.; Krawzoff, M., and McGavack, T. H.: New York J. Med. *58*:520 (Feb. 15) 1958.

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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*Judson, W. E., Hollander, W., and Wilkins, R. W.: Circulation *13*:664 (May) 1956.

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